Cerebral oxygenation in the preterm neonate

Brain Center
Rudolf Magnus

Laura M. L. Dix

Cerebral oxygenation in the preterm neonate

Laura Marie Louise Dix

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Cerebral oxygenation in the preterm neonate

Cerebrale oxygenatie van de vroeggeborene

(met een samenvatting in het Nederlands)

Proefschrift

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Laura Marie Louise Dix

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Promotor
Prof.dr. F. van Bel

Copromotor
Dr. P.M.A. Lemmers

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Introduction

1

CHAPTER I

Introduction

Preterm birth

In an era of advancing technology and therapeutic possibilities, the number of preterm infants (children born before 37 weeks of gestation) and of extremely preterm infants (born before 28 weeks of gestation) are steadily increasing. Today, worldwide, approximately 15 million babies are born prematurely every year.[1] An incidence of preterm birth before 32 weeks of gestation between 10.6 to 17.1 per 1000 births has been reported across Europe, with an average of 13.2 per 1000 births.[2] The Netherlands has one of the lower preterm birth rates with a relatively high mortality rate, presumably due to a policy of restricting treatment in babies born before 24 weeks of gestation.[2] Although survival rates are improving, preterm birth is still associated with significant morbidity.[3] Survival and morbidity are both strongly related to gestational age.[4] Recent literature has indicated infants born at the earliest gestational ages are at an increased risk of neurodevelopmental impairment in early childhood.[5] Complications of preterm birth are the leading cause of mortality in children under 5 years of age. In 2015, mortality in preterm infants was estimated to 1 million worldwide.[1]

Decreasing gestational age is associated with higher rates of complications. Half of the infants born before 27 weeks suffer from major neonatal complications such as necrotising enterocolitis, bronchopulmonary dysplasia, intraventricular haemorrhage and hemodynamically significant patent ductus arteriosus.[6-8] Despite this, the discussion is ongoing whether or not the limit of viability can be pushed back even further. Considering the significant burden of morbidity amongst preterm infants, identification of risk factors and timely interventions are of the utmost importance.

Brain injury

The brain is one of the most vulnerable organs in the neonatal period. The preterm brain in particular is still in full development (see Figure 1) and very much susceptible to injury. During the neonatal period, the brain is maturing in volume and gyri- and sulcification, and connections and networks are being constructed. The developmental status of different brain regions and maturational state of different cell types determine their respective vulnerability. White matter, for example, is especially vulnerable to disturbances in perfusion due to its vascular anatomy being located at the end of the penetrating arterial vessels at the periventricular zone, and the inability to autoregulate cerebral blood flow.[9,10] Also, specific cell types are more vulnerable than others. Oligodendrocyte precursors are more sensitive to injury than mature oligodendrocytes.[11] Brain injury in preterm neonates is common and it is a major predictor of quality of life after the neonatal period and later in life. Although often mentioned as one group, brain injury is rather heterogeneous and entails very different pathologies. Different types of injuries include germinal matrix or peri-intraventricular haemorrhages (PIVH) and infarctions, ischemic and reperfusion injury, white matter injury such as periventricular leukomalacia in a cystic or non-cystic form, and regional or diffuse grey matter injury may be seen.[12,13] The severity of the injury is not only determined by the location and extension of the injury, but also by its effect on nerve tracts and neuronal networks.[14,15] The neonatal clinical presentation of brain injury can vary extremely in the individual infant, from a hyperactivity to lethargy, with or without irritability, and also seizures can indicate neurological injury.

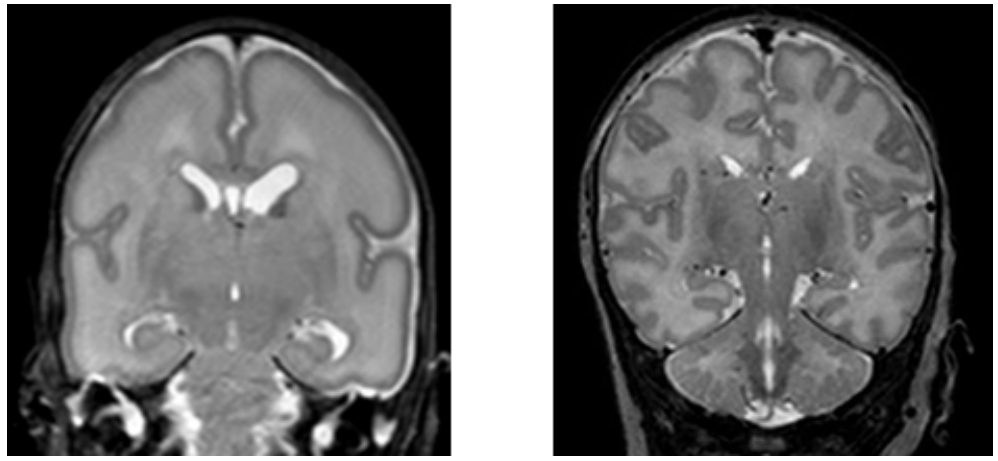

Figure 1. Brain development. T_2 MRI scans of an infant of 30 weeks GA of the left, and 40 weeks GA on the right. Noteworthy is the increase in volume, myelination, gyri- and sulcification.

Injury acquired in the neonatal period can lead to various types of behavioural, attentional, cognitive, language, or sensorimotor impairments and to epilepsy.[13] Many children who were born prematurely show a delay in both motor and cognitive development at school age when compared to their term-born peers, with boys being more affected than girls.[16,17] Both the increasing number of preterm infants as well as increased survival rates contribute to the prevalence of neonatal brain injury.[18,19] Although multifactorial in aetiology, unstable or inadequate perfusion and oxygenation are understood to be important causes. Both hyperoxia, hypoxia and fluctuations in cerebral oxygenation, indicating poor cerebral autoregulatory capacity, have been shown to negatively affect the brain.[12,20,21] The preterm brain is also particularly vulnerable to oxidative injury, due to a relatively high concentration of unsaturated fatty acids, production of free radicals, and accumulation of redox-active iron, in the presence of immature antioxidant defences and

low concentrations of antioxidants.[10,12,22] Additionally, due to its rapid development, the brain is using a substantial amount of oxygen.[23,24]

Insight into the condition of the neonatal brain is vital in order to implement adequate preventive measures and interventions that aim to prevent neurological damage.

Cerebral oxygenation can be affected by several different factors. Cerebral perfusion as well as oxygen metabolism in the brain are dynamic features, resulting in changes in oxygenation. This is especially the case in preterm infants, who are often sick and unstable, susceptible to fluctuations in ventilation and circulation, and unable to autoregulate cerebral blood flow. Autoregulation is the ability to maintain stable perfusion during fluctuations in arterial blood pressure.[25] It is thought to occur over a defined range of arterial blood pressures. Changes in blood pressure within the autoregulatory range, or autoregulatory plateau, do not affect cerebral perfusion. However, in case of hypo- or hypertension, blood pressure overrides the autoregulatory capability, resulting in changes in cerebral perfusion. In preterm infants, the autoregulatory plateau is believed to be smaller than in older children or adults. This is in part due to the relative immaturity of the vascular anatomy and in part to a relatively immature vasomotor regulation.[26] When autoregulation is absent, a pressure-passive cerebral perfusion occurs. Even small changes in arterial pressure may then result in important changes in perfusion.[9] Thus, premature birth goes together with immaturity of cerebral structures and perfusion.

Autoregulation may be further compromised in sick infants. Preterm infants are often sick, suffering from instabilities in blood pressure and requiring mechanical ventilation. This may result in disturbances in oxygen and carbon dioxide partial pressure, increasing their vulnerability to cerebral injury. The presence of infection and inflammation may have an additional damaging effect on the brain. With all this in mind, it is clear that it is vital to monitor the brain of preterm newborn infants, to detect deteriorations early and to prevent injury.

Assessing the brain in the NICU

Because the clinical presentation can be very subtle with varying symptoms, it may be difficult to recognise neurological injury in many babies. This emphasises the importance of repeated and structured evaluation of the brain. Although monitoring vital parameters such as blood pressure, heart rate, and pulse oximetry provide important information concerning the neonate's wellbeing, they do not usually offer direct insight and information concerning the neonatal brain. In the neonatal intensive care unit (NICU),

there are several ways to examine the brain. The basic neurological physical examination is now accompanied by various other diagnostic procedures.

Cranial ultrasounds (cUS) with Doppler flow measurements show anatomical information and identifies intracranial pathology such as haemorrhages, periventricular leukomalacia, ventricular dilatation, and cerebellar lesions.[27] cUS is readily accessible in most NICU's and enables serial examinations. Magnetic resonance imaging (MRI) is an alternative to cUS with regard to anatomical insight, supplying clearer and more detailed images. The disadvantage is that it is time consuming and not readily available in all hospitals. Beside the common anatomical T1 and T_2 sequences, MRI can also include diffusion tensor imaging and tractography, Susceptibility Weighted Image for haemorrhagic lesions, Magnetization Transfer Ratio for white matter integrity, MR Spectroscopy for metabolite analysis, and functional MRI to assess local changes in oxygenation following activity and resting-state networks.[14] Both cUS and MRI are intermittent modalities, which do not provide a continuous assessment of cerebral oxygenation and perfusion.

Continuous monitoring with (amplitude integrated) electro-encephalogram (aEEG) provides information about cerebral electrical activity and background patterns, and is often applied for seizure detection (see Figure 2). Several electrodes are placed over the scalp to measure brain activity. The raw 256Hz EEG signal is used to calculate Spontaneous Activity Transients (SAT). The interval between SATs is the InterSAT Interval (ISI).

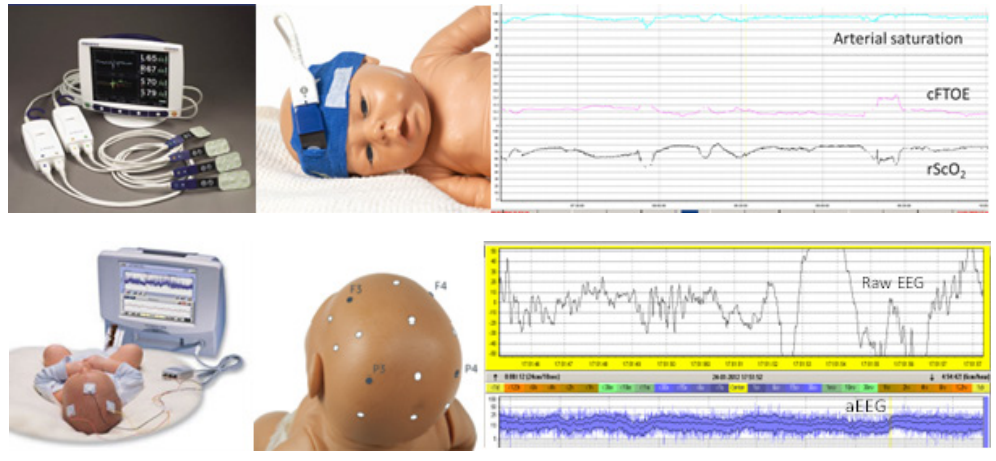

Figure 2. Neuromonitoring. Top panel: near-infrared spectroscopy (NIRS). From left to righ is shown the device, sensor placement, and registration with regional cerebral oxygen saturation ($rScO_2$) and fractional tissue oxygen extraction (cFTOE). Lower panel: electroencephalography (EEG). From left to right is shown the device, needle placement, and registration with the raw EEG and amplitude-integrated EEG signal.

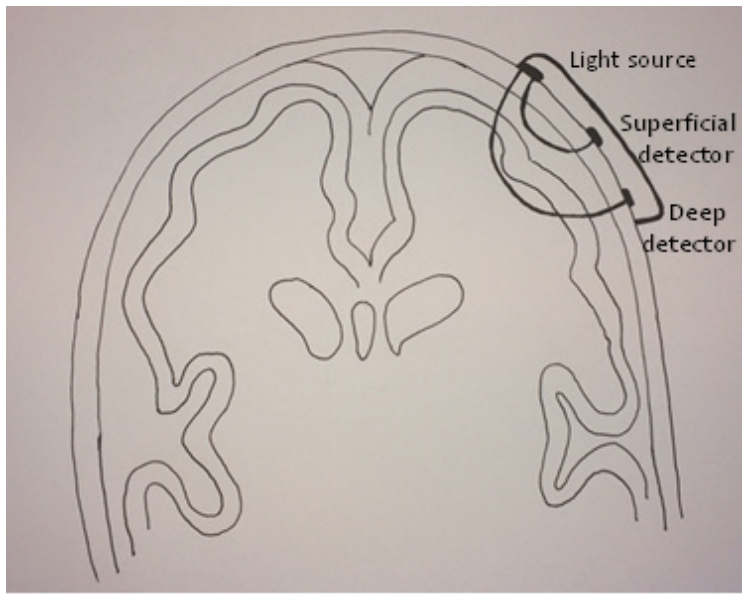

Figure 3. Near-infrared light pathways. The near-infrared bundle from the light source is collected at different distances. A superficial bundle mainly penetrates scalp and skin tissue, whereas the deeper bundle penetrates cerebral tissue. By subtracting the resulting superficial signal from the deeper signal, the influence of scattering on the measurements is reduced.

The number of SATs per minute is a measure of brain activity or function, and inversely is the ISI length. The aEEG signal is an EEG signal that is filtered and compressed in time, and it reflects the background activity pattern of the brain. Several background patterns can be distinguished, such as continuous normal voltage (CNV), discontinuous normal voltage (DNV), burst suppression (BS), low voltage (LV), and flat trace.[28] (a)EEG parameters have also been correlated to outcome in preterm neonates.[29,30] Near-infrared spectroscopy (NIRS) is continuous, non-invasive bedside method to monitor regional cerebral oxygenation as a surrogate of cerebral perfusion (see Figure 2).

Near-infrared spectroscopy

The NIRS technique is based on the relative transparency of biological tissue to Near InfraRed light (700 – 1000nm) light. The first report on the application of cerebral NIRS to measure regional oxygenation *in vivo* was published by Jöbsis.[31] The technique is exceptionally suitable for neonates, as their tissue can be easily penetrated due to thin overlaying layers of skin and skull. Light in the near-infrared spectrum is sent from an

emitter that is fixed to the skull and is collected at some distance from the emitter after passing through the underlying brain tissue. The light beam penetrates approximately 2cm deep into the brain.[32] At specific wavelengths, NIR light is absorbed by oxygenized (O_2Hb) and deoxygenized (HHb) haemoglobin, together accounting for total Hb (THb = O_2Hb + HHb), and by cytochrome aa3. The differences in light absorption are used to calculate the relative concentrations of the haemoglobin and cytochrome chromophores with the modified Lambert-Beer law. The ratio between O_2Hb and HHb is expressed as the regional cerebral oxygen saturation ($rScO_2$) or tissue oxygenation index (TOI), depending on manufacturer. The NIRS signal represents a mixed arterial-venous oxygen saturation, with a relative contribution of arteries of 25%, of capillaries of 5% and of veins of 70%.[33] By applying several detectors, the superficial signal can be distinguished from the desired deeper signal that passes through the cerebral tissue, thus also enabling reduction of the effect of scattering. (See Figure 3). This method is called spatially resolved spectroscopy (SRS). Although there are different techniques, most commercially available devices utilise the continuous wave technique, which measures the attenuation (or absorption) of NIR light from a continuous light source.[34]

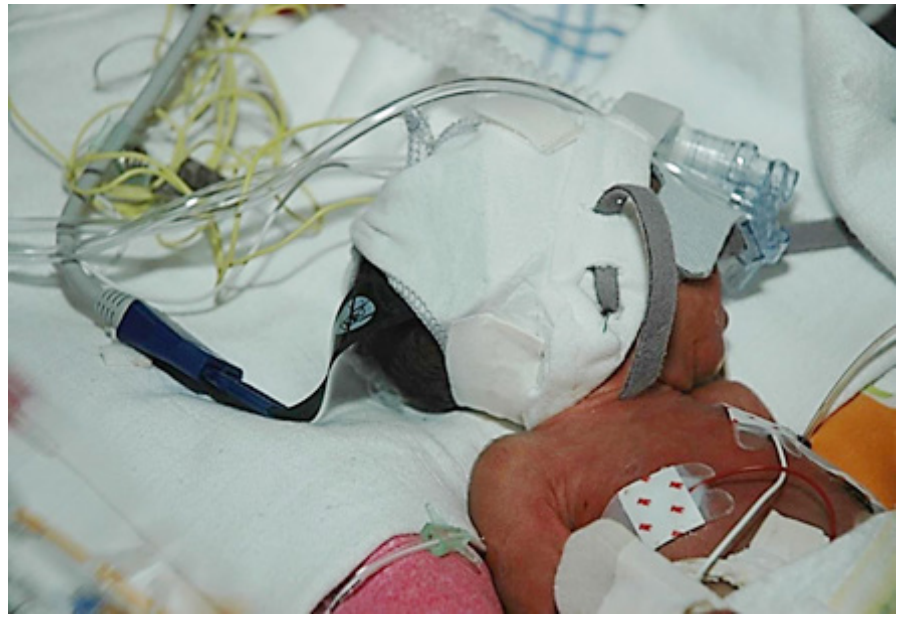

Figure 4. Cerebral oxygenation monitoring in clinical practice. Preterm infant of 25 weeks GA with a NIRS sensor on the fronto-parietal part of the head, covered by a white CPAP hat.

Cerebral oxygenation monitoring with NIRS shows the oxygen saturation of the area below the sensor. This information is important and necessary in order to provide optimal care for unstable and sick newborns in an intensive care setting. It has both diagnostic and prognostic value and aids the clinician in assessing the necessity of interventions.[35] NIRS is an optimal method for monitoring the brain in a non-invasive manner, continuously, and without side effects, and the devices can be used bedside without interfering with care as well as in the operating theatre or during transportation, even in the sickest infants.[36] An example of cerebral oxygenation monitoring is shown in Figure 4.

If we are able to detect deteriorations early and apply appropriate interventions, we hope to avoid situations with unfavourable cerebral homeostasis and prevent cerebral injury, thus improving short-term and long-term neurodevelopmental outcome. As a surrogate of cerebral blood flow and oxygenation, cerebral monitoring with NIRS provides an instantaneous assessment of important parameters of the condition of the brain. Insight into the mechanisms and factors that alter cerebral oxygenation allows the clinician to start implementing preventive measures. Advances in neurological outcome can only be achieved when cerebral injury is prevented in the early neonatal period. The possibility to continuously monitor haemodynamic and oxidative parameters of the neonatal brain is another important step towards this goal.

Outline of this thesis

This thesis contains several research projects which together aim for a better understanding of cerebral oxygenation in preterm neonates and for the use of cerebral oxygenation monitoring in clinical practice. Monitoring cerebral oxygenation is standard clinical care in our hospital during the first 3 days of life in all infants born before 32 weeks of gestation. This period is especially important, as it includes the transitional phase when infants are especially susceptible to neurological injury. Cerebral oxygenation monitoring is also implemented during neonatal surgery or in case of (suspicion of) any neurological defect. Most other hospitals have not implemented neuromonitoring into daily care but only use it is a research tool. This thesis has analysed the patterns of cerebral oxygenation and oxygen extraction in a variety of clinical conditions, to increase our knowledge of cerebral oxygenation during the routine use of cerebral oxygenation monitoring. **Part I** focuses on the technique used to monitor cerebral oxygenation, NIRS. It contains a review, an overview of cerebral oxygenation monitoring in neonates, and two chapters which study the use of NIRS in the neonatal intensive care unit. The following parts of this thesis outline the ways different clinical condition affect cerebral oxygenation and oxygen extraction in the brain of preterm neonates. **Part II** investigates the effects of a patent ductus arteriosus, **part III** evaluates fluctuations in carbon dioxide partial pressure,

and **part IV** focuses on the effects of caffeine. All studies were performed with the INVOS near-infrared spectrometer (Covedien, Mansfield, MA USA) with the small adult sensor (small adult SomaSensor SAFB-SM, Covidien, Mansfield, MA, USA), unless otherwise specified.

Part I. Near-infrared spectroscopy

Fortunately, the use of NIRS to monitor cerebral oxygenation is increasing throughout the world. **Chapter 2** is a review highlighting the different clinical applications of monitoring cerebral oxygenation in neonates at an intensive care unit, focusing on recent advances and reports from the literature.

The increased clinical interest in monitoring cerebral oxygenation with NIRS in neonates, has given a boost to the technique and led to the development of new devices and sensors. These developments have increased user-friendliness, especially in the smallest patients. Adaptations to sensors for instance include smaller design, higher flexibility, and improvement of sharp edges to protect the easily damaged skin of newborns. In **chapter 3** we compared several of these new devices and sensors in measuring cerebral oxygenation in neonates in an intensive care unit.

One of the main limitation of the universal application of cerebral oxygenation monitoring with NIRS in NICU's was lack of robust and reliable reference values based on a large cohort of patients with varying gestational ages (GA). In **chapter 4**, reference values for cerebral oxygenation monitoring with NIRS are provided for preterm neonates, subdivided into GA groups between 24 up to 32 weeks. We created reference value curves per GA groups for bedside interpretation of values, for both the small adult and neonatal sensor. Moreover, we estimated the effects of several clinical parameters, such as gender and patent ductus arteriosus.

Part II. Patent ductus arteriosus

A hemodynamically significant patent ductus arteriosus (hsPDA) is a highly common complication of preterm birth, with an increasing incidence with decreasing GA. Ductal shunting can adversely affect cerebral perfusion and oxygenation, with the lowest values is infants who require surgical closure of the duct.[37] In **chapter 5**, we prospectively analysed cerebral oxygenation and echocardiographic analysis of the duct during the first week of life.

Small-for-gestational-age infants (SGA) are infants who are born with a birth weight too low for their respective gestational age, often due to intra-uterine growth restriction (IUGR). During this period of IUGR, blood perfusion is redistributed to vital organs, such as the brain. This is called the brain-sparing effect.[38] As a result of this redistribution, SGA infants are born with higher cerebral oxygenation values than their appropriately-grown peers. However, this luxury perfusion does not seem to protect them from negative influences on cerebral oxygenation. In **chapter 6** we have analysed the effect of a hsPDA on cerebral oxygenation in SGA infants, compared to appropriately-grown infants.

Carbon monoxide (CO) is a marker of inflammation, and can be measured in exhaled air in preterm infants. CO can affect cerebral perfusion by inducing vasodilatation. In **chapter 7** we report on a study of the predictive value of end-tidal carbon monoxide on the first day after birth for the development of a hsPDA, as well as its relation to cerebral oxygenation.

The hsPDA remains subject of debate in neonatology. A hsPDA has been associated with several neonatal complications, such as bronchopulmonary dysplasia, intracranial haemorrhage, pulmonary edema, bronchopulmonary dysplasia, and necrotising enterocolitis.[39] There is an ongoing debate whether or not a hsPDA is causative factor in these associations, or if they are all manifestations of the sickness and instability that are so common to preterm neonates. Therefore, there is no consensus on the best treatment at this time. In **chapter 8** we have analysed the neurodevelopmental outcome at 2 years and at 5 years of preterm infants with and without a hsPDA, with a subdivision between medically treated and surgically treated hsPDA's.

Part III. Carbon dioxide

Cerebral perfusion and oxygenation can be easily influenced by several external factors, due to immaturity of cerebrovascular bed and the inability to autoregulate cerebral blood flow. Carbon dioxide (CO_2) is one of the main factors that has an effect on the cerebral arteries, where hypercapnia induces vasodilatation and hypocapnia results in vasoconstriction. Fluctuations in CO_2 are common in ventilated infants. In **chapter 9** the effects of acute changes in CO_2 on the neonatal brain are studied, including both cerebral oxygenation as well as electrical brain activity measured with EEG.

Extremely high levels of CO_2 have been associated with neuronal depression and even coma in adults. Although fortunately uncommon, severe hypercapnia also occurs in preterm neonates. CO_2 can affect electrical brain activity as well as oxygenation. **Chapter 10** shows the results of an observational study analysing the effects of severe hypercapnia on the aEEG background pattern and cerebral oxygenation.

Part IV. Caffeine

The relative immaturity of the respiratory centre in preterm infants can result into apnea of prematurity (AOP), a temporary cessation of respiration often accompanied by a decrease in SaO_2 and by bradycardia. AOP is often treated with caffeine, a methylxanthine that acts as a adenosine antagonist. By blocking the inhibiting effect of adenosine, caffeine stimulates respiration in several ways. Studies have shown a potential neuroprotective effect of caffeine. In **chapter 11** we have analysed the effects of caffeine for the prevention of AOP on the brain of preterm neonates, including both cerebral oxygenation, electrical activity, as well as perfusion.

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PART 1

NEAR-INFRARED SPECTROSCOPY

Monitoring cerebral oxygenation in neonates: an update

Laura M. L. Dix[1,2], Frank van Bel[1]
Petra M. A. Lemmers[1]

[1] Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands.
[2] Monash Newborn,Monash Medical Centre, Melbourne, VIC, Australia

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CHAPTER 2

Monitoring cerebral oxygenation in neonates: an update

Abstract

Cerebral oxygenation is not always reflected by systemic arterial oxygenation. Therefore, regional cerebral oxygen saturation ($rScO_2$) monitoring with near-infrared spectroscopy (NIRS) is of added value in neonatal intensive care. $rScO_2$ represents oxygen supply to the brain, while cerebral fractional tissue oxygen extraction, which is the ratio between $rScO_2$ and systemic arterial oxygen saturation, reflects cerebral oxygen utilization.
The balance between oxygen supply and utilization provides insight in neonatal cerebral (patho-)physiology. This review highlights the potential and limitations of cerebral oxygenation monitoring with NIRS in the neonatal intensive care unit.

Introduction

It has been nearly 8 years, since our research group published a review on the value and pitfalls of cerebral oxygenation monitoring with near-infrared spectroscopy (NIRS) in neonatology.[1] Since then, research into cerebral NIRS has taken an impressive flight. The importance of cerebral oxygenation and perfusion monitoring has been increasingly recognized in neonatal intensive care. In this review, the development of cerebral NIRS monitoring over the past years is summarized.

Value of cerebral oxygenation monitoring

Unfortunately, brain injury is still common in preterm neonates and can lead to a wide range of complications later in life, such as behavioral, attentional, cognitive, sensorimotor or language impairments, and epilepsy.[2] Both the increasing number of preterm infants and improved survival rates contribute to the prevalence of neonatal brain injury.[3,4] Preterm infants are particularly susceptible to brain injury as the brain undergoes rapid development during the last trimester of pregnancy. During this period, the brain does not only increase in volume but also undergoes increasing gyri- and sulcification and myelination and improves connectivity.[5] Preoligodendrocytes and axons mature, the transient subplate neurons appear, and the cerebellum develops and matures. Throughout this process, the brain is using substantial amounts of oxygen.[2,6,7] Cerebral pathology can present as white matter injury, such as periventricular leukomalacia, or as periventricular–intraventricular hemorrhage (PIVH).Inadequate or fluctuating cerebral perfusion and oxygenation can result in brain injury.[8] Hyperoxia, hypoxia, and fluctuations in cerebral oxygenation, indicative of poor cerebral autoregulation, can adversely affect brain development.[9–12]

Vital parameters such as blood pressure, heart rate, and pulse oximetry [arterial oxygen saturation (SaO_2)] are important to assess the condition of the neonate but do not directly assess brain oxygenation.[13,14] NIRS-monitored regional cerebral oxygen saturation ($rScO_2$) is a non-invasive and elegant method to monitor global brain oxygenation. $rScO_2$ monitoring can be used at bedside for extended periods of time (up to several days) without side effects. Other methods that examine the brain, such as cranial ultrasound or MRI, do not allow for continuous monitoring. NIRS can be used even in the sickest infants and requires minimal handling of the infant. The device can be used at bedside in the NICU as well as during surgery or transportation.[15] NIRS can easily be combined with monitoring of cerebral electrical activity by amplitude-integrated electro-encephalography (aEEG).

NIRS technique

The NIRS technique is based on the relative transparency of biological tissue to light. Neonatal cerebral tissue can easily be penetrated by NIR light (700–1,000 nm) due to thin overlaying layers of skin and skull. An emitter sends light of the near-infrared spectrum through cerebral tissue in a semi-curved shape to a detector, approximately 2–3 cm in depth.[16] Oxygenated (O_2Hb) and deoxygenated (HHb) hemoglobin absorb the NIR light at different wavelengths, together accounting for total Hb (THb = O_2Hb + HHb). Differences in NIR light absorption are detected by the sensor and used to calculate the concentrations of Ohb and HHb according to the modified law of Lambert–Beer. The ratio between O_2Hb and HHb is expressed as the $rScO_2$ or tissue oxygenation index (TOI), depending on the manufacturer of the NIRS device. Previous research has shown good correlation between TOI and $rScO_2$.[17,18] The NIR light is absorbed by HHb and O_2Hb in both arterial and venous vessels, in a 25:75% ratio, and thus NRS reflects mainly cerebral venous oxygen saturation.[19] The NIR light is absorbed by both superficial tissues and the cerebral cortex. When two or more detectors are used, the deeper signal reflecting cerebral cortex oxygenation can be distinguished from the superficial signal, reducing the influence of scattering. The technical details of NIRS are beyond the scope of this review but are well described elsewhere.[20–23] Most commercially available devices utilize the continuous-wave technique, which measures the attenuation (or absorption) of NIR light from a continuous light source to calculate oxygenation.[24] Other NIRS techniques, such as time-resolved spectroscopy and frequency-resolved spectroscopy, are now able to assess cerebral blood volume and quantify absolute concentrations of HHb and O_2Hb, respectively. However, these techniques have not yet been proved practically useful in neonatal care.[24]

Sensors and devices

Today, there are several different NIRS devices and sensors commercially available. A number of comparative studies have shown that the overall correlation between NIRS devices is acceptable, although they differ in technique and algorithm.[25–27] Smaller and more flexible sensors have been designed for neonatal use. However, these neonatal sensors measure 10% higher compared to the adult sensors.[28,29] Since the upper limit of most devices is set to 95%, high cerebral oxygenation values as measured by the neonatal sensors are shown as a flat line in which all variation is lost, as demonstrated in Figure 1A. NIRS device and sensor type must be taken into account when NIRS monitoring of cerebral oxygenation is applied in clinical care. Reference values for the neonatal sensor have been published (see below).[29]

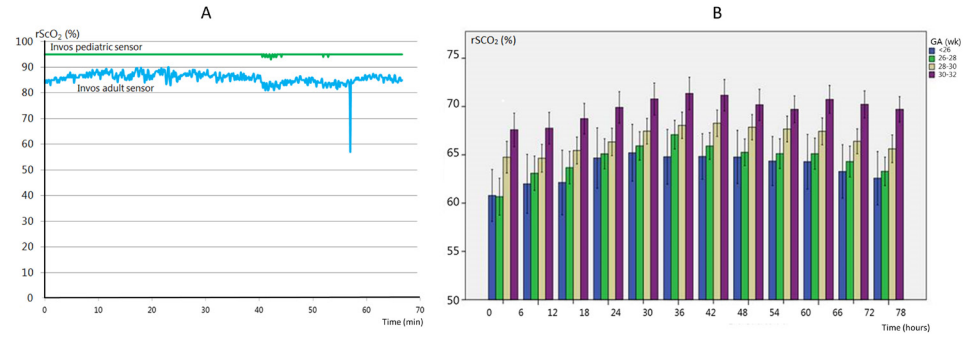

Figure 1. [A] Regional cerebral oxygen saturation ($rScO_2$) monitored with and adult (blue line) and pediatric (green line) sensor. Hyperoxia values are untraceable with the pediatric sensor due to the cutoff value of 95%. [B] Reference values [stratified for gestational age (GA)] of $rScO_2$ in premature infants (GA<32 weeks). Adapted from reference 29.

Validation

Regional cerebral oxygen saturation represents a mixed saturation largely determined by the venous component (75%), which is why NIRS validation studies have often focused on venous saturation.[19] However, venous saturation does not reflect mixed arterial and venous saturation as NIRS does, and there is no "gold standard" to measure venous oxygen saturation.[30] A good correlation has been reported between oxygen saturation in the jugular vein and NIRS-monitored cerebral oxygenation, with a mean difference of 5%, for different manufacturers (Hamamatsu, INVOS, CAS-MED).[31–34] However, the difference between jugular venous oxygen saturation and regional cerebral oxygenation may increase during hypoxia. This is presumably caused by an increased arterial contribution to the NIRS signal due to cerebral arterial vasodilatation as a response to hypoxia.[35] Cerebral fractional tissue oxygen extraction (cFTOE) has been validated against central cerebral venous saturation in newborn piglets.[36] Brain perfusion assessment with NIRS has been compared to perfusion assessment with MRI, which has shown strong correlations.[37,38] Both $rScO_2$ and TOI have shown good reproducibility.[39,40]

Reference values

Several studies have analyzed changes in $rScO_2$ with advancing postnatal age. $rScO_2$ is between approximately 40 and 56% directly after birth (irrespective of delivery mode)[41–43] increases up to 78% in the first 2 days after birth[44] and then slowly stabilizes during 3–6 weeks after birth with values between 55 and 85%.[45–47] Several studies have published reference ranges immediately after birth, which show a gradual increase during the first

15 min of life.[42,46] A recent study by Alderliesten et al. provides reference values based on a large study cohort during the first 72 h of life in preterm infants [<32 weeks gestational age (GA); n = 999]. The data are converted into reference curves stratified for different GAs which can be used for cot side interpretation of $rScO_2$ and cFTOE values, as shown in Figure 1B.[29] These reference values, obtained with the (small) adult sensor (SomaSensor SAFB-SM, Covidien, Mansfield, MA, USA), will facilitate clinical application of cerebral oxygenation monitoring. As stated above, it is important to realize that neonatal sensors of various NIRS manufacturers display higher values (up to 10%) as compared to adult sensors.[28]

Clinical application

Gaining insight into the oxygenation of the neonatal brain can be of important clinical value, as a large share of neonatal pathology is brain associated. NIRS monitoring of cerebral oxygenation can be considered in several clinical situations as outlined below.

Cerebral oxygenation and the patent ductus arteriosus

The hemodynamically significant patent ductus arteriosus (PDA) remains a controversial topic. Clinicians and researchers are still debating whether or not it should be treated, what the best treatment strategy is and when would be the best time to intervene.[48-50] Unfortunately, the brain is rarely included in this discussion. A PDA can negatively influence cerebral oxygenation. Shunting of the blood through the duct away from the brain has a profound negative effect on $rScO_2$. This effect is independent from SaO_2, which remains within normal limits during a PDA.[13, 51] Cerebral oxygenation normalizes after ductal closure.[13,51] The ductal diameter is associated with cerebral oxygenation, where a larger diameter (indicating a significant left to right ductal shunt) is associated with lower $rScO_2$.[51] Infants who need surgical PDA closure are often exposed to low $rScO_2$ values for a longer period of time, as shown in Figure 2A, and are therefore at risk of cerebral injury.[14] Additionally, a further reduction in cerebral oxygenation occurs during ductal surgery.[52,53] Weisz et al. reported an increased risk of neurodevelopmental impairment in infants after surgical ductal ligation compared to pharmaceutically treated infants.[54] More specifically, underdevelopment of the cerebellar structure has been reported in infants who needed surgical closure.[14] Extended episodes of low cerebral oxygenation are most likely responsible for this phenomenon.[14]

Cerebral oxygenation and respiration

Preterm infants often require respiratory support, which can affect cerebral hemodynamics and cerebral oxygenation.[55,56] An earlier study reported NIRS-monitored changes in cerebral blood flow (CBF) during continuous positive airway pressure and artificial ventilation. CBF significantly correlated with the type of respiratory support, leading to the conclusion that ventilation can impact cerebral circulation.[57] Cerebral oxygenation can also be affected by the type of ventilation support during surgery.[58]

Ventilation is the main regulatory mechanism of arterial carbon dioxide pressure (pCO_2). pCO_2 can affect the brain by altering cerebral arterial vessel diameter, where hypercapnia can induce cerebral vasodilatation and hypocapnia induces vasoconstriction.[59] As such, pCO_2 can affect cerebral perfusion and oxygenation, and both hyper- and hypocapnia have been associated with neuropathology.[60,61] An increase in pCO_2 is accompanied by an increase in cerebral oxygen saturation with a decrease in oxygen extraction.[62,63] Acute fluctuations in pCO_2, even within the normal range, appear to directly affect the neonatal brain perfusion (personal communication). The pCO_2-induced changes in cerebral perfusion and oxygenation can be monitored by NIRS, as shown in Figure 2B, in order to identify and prevent pCO_2-induced cerebral hypo- or hyperperfusion and brain damage.

Other factors related to respiration have also been shown to influence cerebral oxygenation. Apneas, for example, can affect brain oxygenation, and high mean airway pressure during artificial ventilation can also reduce cerebral oxygenation.[1,64–66] Also, infants with respiratory distress syndrome (RDS) have lower cerebral oxygenation and increased variance in $rScO_2$ and cFTOE during the first 3 days after birth.[67,68] Moreover, they often have an impaired cerebral autoregulation, which may further predispose them to cerebral injury.[69] Combining arterial blood pressure and cerebral oxygenation measures can help to identify (lack of) cerebral autoregulation (see below).

Cerebral oxygenation and autoregulation

Cerebral autoregulation is the ability to maintain stable cerebral perfusion and oxygenation during fluctuations in blood pressure.[70] Hypotension can cause a severe reduction in cerebral perfusion and impairment of cerebral autoregulation, leading to inadequate perfusion.[71] Combining $rScO_2$-monitoring with arterial blood pressure monitoring enables assessment of cerebral autoregulation.[72] Prematurity is a risk factor for impaired autoregulation, and even small variations in blood pressure can affect cerebral oxygenation in clinically sick and unstable babies.[73,74] Cerebral autoregulation can indeed be affected in several clinical situations that are commonly seen in preterm infants. Our group has previously demonstrated that RDS predisposes for lack of cerebral autoregulation.[69] Autoregulation might also be impaired during surgery and high concentrations of positive inotropes such as dopamine.[11,75] Impaired autoregulation has been linked to poor neurodevelopmental outcome.[76] Evaluating cerebral autoregulation at bedside can identify episodes of impaired autoregulation, and appropriate measures can be initiated to stabilize cerebral perfusion and oxygenation. Cerebral autoregulation can be computed in different ways, and software to calculate autoregulation at bedside is currently being developed.[77] In summary, cerebral autoregulation may become impaired, especially in the unstable (preterm) infant, predisposing these neonates to brain injury. This underlines the importance of cerebral oxygenation an autoregulation monitoring in the early neonatal period.[78]

Cerebral oxygenation and hypotension

Cerebral oxygenation can play an important role in assessing hypotension and whether positive inotropic therapy is indicated. There is an increasing awareness that the current definitions of hypotension of prematurity do not always reflect true hypotension. Permissive hypotension is increasingly accepted, unless there are (clinical) signs of hypoperfusion.[79-81] As already stated above, hypotensive treatment is not without side effects and may have adverse effects on outcome.[11,82] Cerebral oxygenation plays an important role as a marker of end-organ oxygenation and can help making decisions whether or not treatment for hypotension is indicated. Other parameters such as blood gasses, urine production, and capillary refill should be taken into account. Identifying small reductions in blood pressure that do not affect cerebral oxygenation, and systemic perfusion might prevent unnecessary treatment with inotropes.[81,83] Monitoring $rScO_2$ and cerebral autoregulation during neonatal surgery is important to prevent hypotension-related injury to the immature brain (see also below).[84] Our research group is currently involved in a prospective study (the TOHOP study) to find an answer to the question at which stage hypotension treatment is warranted (TOHOP; http://ClinicalTrials.gov identifier: NCT01434251).

Cerebral oxygenation and small-for-gestational-age (SGA) neonates

Preterm infants who are born SGA show higher cerebral oxygenation during the first postnatal days.[29,85] This is most likely related to the prenatal blood flow redistribution of the intrauterine growth restricted (IUGR) fetus, in an attempt to preserve oxygen supply to the brain (brain sparing effect).[86] However, this does not necessarily protect against cerebral injury, and infants born following IUGR are at an increased risk of neurodevelopmental impairment.[87,88] In case of a PDA, SGA infants demonstrated a significantly larger fall in cerebral oxygenation, as compared to AGA infants.[89]

Cerebral oxygenation and neurodevelopmental outcome

Disturbances in cerebral perfusion and oxygenation are major contributors to neonatal brain injury, increasing the risk of impaired neurodevelopmental outcome.[8,90] Infants are particularly susceptible to brain injury during the first 3 days after birth, when major hemodynamic transitional changes occur. A large international randomized controlled trial, the SafeboosC study (Safeguarding the brains of out smallest children), has investigated whether it is possible to reduce the hypoxic and/or hyperoxic burden on the immature brain with cerebral oxygenation monitoring, in order to prevent neurological damage and to improve outcome.[91] The study has shown that disturbances in cerebral oxygenation could be identified with NIRS. A treatment protocol prescribed treatment steps to restore normal brain oxygenation. The burden of hypoxia (and hyperoxia), as expressed by the percentage of time spend outside the normal range of $rScO_2$ (55–85%), was significantly lower in the group with (visible) NIRS monitoring as compared to the blinded control group (median 36.1 vs. 81.3%).[47] This difference was mainly due to a reduction in hypoxic episodes.

Impaired cerebral oxygenation below the threshold of 55% appears to affect neurodevelopmental outcome at 15 and 24 months corrected age (personal communication). Poor cerebral autoregulation, examined by the correlation between $rScO_2$ and arterial blood pressure, has been be associated with an increased risk score predictive of neonatal mortality and morbidity (CRIB II).[92]

Several studies, in newborn animals and humans, showed that $rScO_2$ values consistently below 40% (measured with adult sensors) are related to brain damage.[93–95] Other clinical studies showed that low cerebral oxygen saturation immediately after birth (<15 min) is associated with PIVH.[96] In accordance with these results, low cerebral oxygenation during the first 48 h after birth was associated with death or severe PIVH in a study by Cerbo et al.[97] Similarly, increased oxygen extraction cFTOE can precede development of PIVH.[98,99]

Cerebral oxygenation and red blood cell transfusions

Several studies have shown a significant increase in cerebral oxygenation after red blood cell transfusions in anemic infants.[100,101] The infants with the lowest pre-transfusion $rScO_2$ values seem to benefit the most from transfusions.[102] Similarly, high cFTOE levels (>0.4) can indicate an imbalance between cerebral oxygen supply and demand, which may underline the need for red blood cell transfusion.[103] This indicates that cerebral oxygenation monitoring might be useful as a marker to identify infants with high cFTOE and/or low $rScO_2$ who might benefit from blood transfusions.[103–105]

Cerebral oxygenation and neonatal surgery

Infants with cardiac or non-cardiac anomalies may require major surgery in the first few months after birth.[106] Exposure to neonatal surgery can put the immature brain at risk.[107,108] An increased risk of neurodevelopmental delay after neonatal surgery has indeed been reported.[109,110] Both the procedure as well as anesthetics can be harmful.[111–113] Monitoring cerebral oxygenation during surgery to increase cerebral safety is therefore advised.[114–119] Perioperative monitoring evaluates brain oxygenation pre- and postsurgery, while intraoperative monitoring can assist surgeons and anesthesiologists to optimize cerebral oxygenation during the procedure to protect the neonatal brain.[116,120, 121] During surgery, cerebral NIRS can detect episodes of hypoxia more reliably than arterial SaO_2 monitoring.[117,122] Introduction of cerebral oxygenation monitoring during cardiac surgery has improved intraoperative transfusion management.[123] Cerebral oxygenation monitoring can also reflect changes in vital parameters during cardio-pulmonary bypass.[124]

Cerebral oxygenation and hypoxic-ischemic encephalopathy (HIE)

Previous studies have demonstrated that $rScO_2$ is increased and cFTOE is decreased during the first days after severe birth asphyxia, and these findings have been correlated with an adverse outcome at 2 years of age (Griffiths Mental Developmental scales).[125,126] See also Figure 2C. NIRS monitoring combined with simultaneous assessment of aEEG background patterns has a strong prognostic value for long-term neurodevelopmental

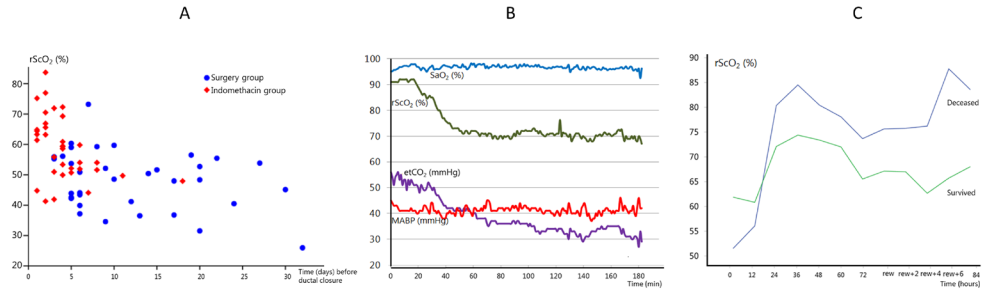

Figure 2. A) Regional cerebral oxygen saturation ($rScO_2$) just before ductal closure in patients treated with indomethacin (red squares) or surgery (blue circles) as a function of postnatal age in days. Note that the majority of infants requiring surgical treatment are exposed to the lowest $rScO_2$ values for a longer period. Adapted from reference 14. B) Acute end-tidal CO_2 ($etCO_2$) decrease results in a subsequent reduction in $rScO_2$, on the contrary arterial oxygen saturation (SaO_2) remains stable. MABP, mean arterial blood pressure.C) $rScO_2$ during hypothermia and after rewarming (rew) in two severely asphyxiated infants. The infant with an adverse outcome (blue line) showed higher $rScO_2$ values compared to the infant that survived (green line). Cerebral fractional tissue oxygen extraction values (not shown) mirrored $rScO_2$ values.

outcome. High cerebral oxygenation with an abnormal aEEG background pattern (low electrical activity) in severely asphyxiated neonates with hypothermia treatment at 12 h of age has a positive predictive value of 91%, absence of these results in a negative predictive value of 100%.[126] These findings strongly suggest that NIRS monitoring of cerebral oxygenation can have an important role in the (early) prognosis of neurodevelopmental outcome. Cerebral hyperoxygenation in neonates with an adverse outcome is most likely explained by low energy metabolism after severe brain injury with low oxygen utilization, cerebral hyperperfusion, and impaired autoregulation of the cerebral vascular bed.[127,128] These findings have been confirmed in other studies, incorporating MRI.[129] Cerebral oxygenation with NIRS correlates strongly with CBF as assessed by arterial spin labeled MRI in infants with severe HIE.[37]

Limitations

Hair, dark skin, and interfering light from other sources such as phototherapy devices can pose a problem during NIRS monitoring.[1] Subdural edema or hematoma below the sensor might also interfere with measurements.[130] In small infants, placement of the electrode might be challenging if they also require simultaneous aEEG monitoring. The curvature of the skull and head circumference has been mentioned as potential limitations.[24] However, Alderliesten et al. did not find a correlation between head circumference and $rScO_2$, stating that influence of head curvature seems unlikely.[29] As previously discussed, type of NIRS device and sensor must be taken into account when interpreting cerebral oxygenation values.[28]

Conclusion

Injury to the immature brain remains a major contributor to neonatal mortality and morbidity. Monitoring vital parameters provides us with critical information concerning the condition of the infant but does not offer direct information regarding brain oxygenation and perfusion. Cerebral oxygenation monitoring with NIRS, at least during the vulnerable transition period throughout the first 3 days after birth, provides the clinician with additional important information. Several clinical conditions can affect brain oxygenation, and studies have shown that systemic oxygen saturation does not always reflect cerebral oxygenation. The assessment of neonatal brain oxygenation (and perfusion) can be extremely useful in the clinical setting. It has the potential to guide clinical management in order to prevent brain injury and to avoid unnecessary treatment. It may also provide important information regarding the infant's prognosis.

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3

Comparing near-infrared spectroscopy devices and their sensors for monitoring regional cerebral oxygen saturation in the neonate

Laura M. L. Dix, Frank van Bel
Willem Baerts, Petra M. A. Lemmers

Department of Neonatology, Wilhelmina Children's Hospital
University Medical Center Utrecht, Utrecht, The Netherlands

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CHAPTER 3

Comparing near-infrared spectroscopy devices and their sensors for monitoring regional cerebral oxygen saturation in the neonate

Abstract

Background Near-infrared spectroscopy (NIRS) is an upcoming clinical method for monitoring regional cerebral oxygen saturation ($rScO_2$) in neonates. There is a growing market offering different devices and sensors. Even though this technique is increasingly clinically applied, little is known about the similarities and/or differences in $rScO_2$ values between the different devices and sensors. The aim of this study was to compare the $rScO_2$ values obtained in (preterm) neonates with all available sensors of three frequently used NIRS devices.

Methods Fifty-five neonates admitted to our neonatal intensive care unit (NICU) were included in this study. $rScO_2$ was simultaneously monitored bilaterally with two different NIRS sensors (left and right frontoparietal) for at least 1 h. Then, the sensors were switched, and measurements were collected for at least another hour.

Results We detected a rather close correlation between all investigated sensors from the three different NIRS devices, but absolute $rScO_2$ values showed substantial differences: Bland–Altman analysis showed average differences from 10 to 15%.

Conclusion Although the $rScO_2$ values correlated well between different NIRS sensors, sometimes there were substantial differences between the absolute $rScO_2$ values, which may complicate clinical application.

Introduction

Investigating and monitoring the neonatal brain provides us with important clinical information. Besides continuous electroencephalogram monitoring, cranial ultrasound, magnetic resonance imaging, and magnetic resonance spectroscopy, near-infrared spectrometry (NIRS)-monitored regional cerebral oxygen saturation ($rScO_2$) is increasingly used.[1-3] NIRS is a noninvasive, bedside technique which can be used to monitor mixed cerebral saturation, which correlates well with venous jugular bulb saturation[4-6] and estimates oxygen supply to the brain.[1,2] Normal values of $rScO_2$ in the neonatal brain are reported to range from 55 to 85%.[2,4-6]

NIRS-monitored $rScO_2$ cannot be used as a robust quantitative measure, given the large inter- and intrapatient variability.[7] However, $rScO_2$ provides us with absolute values, and movement artifacts have a minor influence, which facilitates its ease of use in clinical practice as a trend-monitoring device, analog to arterial saturation (SaO_2) monitoring.[8-10] A study of Menke et al[11] using the Critikon 2000 device (Critikon, Tampa, FL) showed that $rScO_2$ could be determined with an acceptable reproducibility, whereas a study of Sorensen et al[12] using the NIRO 300 device (Hamamatsu Photonics, Hamamatsu, Japan) showed a precision of cerebral saturation measurements (as represented by the tissue oxygenation index or TOI) of ~5.2%.

NIRS has shown its usefulness in multiple studies, it can function as an additional tool to detect a hemodynamically significant patent ductus arteriosus and the effects of (non) invasive ductal closure and as an important prognostic tool after severe perinatal asphyxia and (cardiac) surgery.[13-16] When NIRS is combined with arterial blood pressure monitoring, the correlation between $rScO_2$ and mean blood pressure can also be used to assess autoregulation of the cerebral arterial circulation.[17]

To expand the use of NIRS in neonatal care, it is important that different NIRS devices provide similar results. Grubhofer et al.[18] compared the INVOS 3100 (Somanetics, Troy, MI) and NIRO 500 (Hamamatsu Photonics) devices during and after hypocapnia. Although the overall correlation between the two devices was significant, changes in cerebral hemoglobin oxygenation state were more accurately measured by the INVOS 3100. Cho et al[19] studied the INVOS 3100 and NIRO 500. In addition, Yoshitani et al[6] compared the INVOS 4100 (Somanetics) with the NIRO 300. Generally, the responses of the INVOS and NIRO devices to the cerebral oxygenation changes seem to be similar with a slightly stronger response by the NIRO device. Moreover, these devices show a positive correlation in response to a CO_2 challenge test. However, Bland–Altman analysis revealed bias in the latter study in both absolute values and the percentage of changes.

This indicates that measurements were not quite equivalent and varied depending on the chosen NIRS device and that different NIRS devices provide us with $rScO_2$ values which correlate on average closely, but absolute $rScO_2$ values may (although slightly) differ between different devices.

In neonatal studies of NIRS-monitored $rScO_2$, the NIRS sensors are, until now, the same as those used on adults. Because of the emerging use of NIRS-monitored $rScO_2$ in the often sick and/or unstable (preterm) neonates, most NIRS-device suppliers are developing pediatric and neonatal sensors that are smaller and more suitable for the smaller heads. We earlier reported that pediatric and neonatal sensors provided us with substantially higher $rScO_2$ values as compared with adult sensors, although they correlated well with each other.[20] Differences in technical aspects such as different algorithms, near-infrared light emission source, number of wave lengths, or scattering subtraction may be underlying causes. However, for clinical purposes, it is important to define the normal range of $rScO_2$ values in the (preterm) neonate. A prerequisite for this is that new devices and sensors provide similar results. Comparing the NIRS devices and sensors is therefore much needed and relevant.

The aim of this study was therefore to compare the $rScO_2$ values obtained by different sensors of three frequently used NIRS devices in the neonatal setting.

Methods

Sixty-seven neonates without severe illness or respiratory failure admitted to the NICU of the Wilhelmina Children's Hospital in Utrecht, The Netherlands, were measured bilaterally (left and right frontoparietal) NIRS-determined $rScO_2$. Fifty-five infants provided us with representative measurements. The average gestational age was 30.7 ± 3.9 weeks and birth weight 1,562 ± 886 g. Measurements were considered as nonrepresentative when differences exceeded 30%, when abundant artifacts were present, or when a stable monitoring period of 1 h could not be accomplished.Informed consent was obtained, and the study was approved by the Institutional Review Board of the Wilhelmina Children's Hospital in Utrecht. Obstetric and intrapartum data were collected from the hospital records. Neonatal data were collected prospectively. The attending neonatologist made all clinically important decisions.

NIRS-determined $rScO_2$ was used as an estimator for changes in cerebral oxygenation. When an infant was treated with phototherapy, an extra covering sheet was placed over the sensor to prevent the therapeutic light from affecting the $rScO_2$ measurements.

Three frequently used NIRS devices in the NICU—the INVOS 5100C (Covidien), the Equanox model 7600, and the Fore-Sight systems—were compared.

The INVOS 5100C (Covidien) sensors use light-emitting diodes to emit near-infrared light of two wavelengths (730 and 810 nm). The nature and quantity of the recaptured near-infrared light reflects the amount of HHb and O_2Hb, used to calculate $rScO_2$. Two detectors are located next to the light-emitting diodes. By subtracting the shallow (shorter) signal from the deeper (further) signal, surface interference contamination is minimized.[31,32] Clinical applicability of the INVOS device in neonates has been researched.[33] The INVOS 5100C (Covidien) can be used with three different sensors: the adult (SomaSensor SAFB-SM), pediatric (SomaSensor SPFB), and neonatal sensor (Oxyalert CNN). As the adult sensor has been exclusively used at the Wilhelmina Children's Hospital in the clinical setting, this sensor serves as reference measurement.

The Equanox model 7600 uses two light-emitting diodes (Classic Sensor 8000CA), sending out a near-infrared signal composed of three wavelengths (730, 810, and 880 nm). The two light-emitting diodes are in the middle of the sensor, flanked by two photo diodes to capture the reflected light. Double detectors reduce intervening tissue and surface effects. At the time of the study, no neonatal sensor for the Equanox device was available. The Equanox device has thus far only one (adult) sensor.

The Fore-Sight tissue oximeter and its neonatal sensor (small sensor) use four different wavelengths in the near-infrared light spectrum (from 670–780–805–850 nm). One light emitting source is placed next to an absorbing diode. An overview of the different devices and their sensors is shown in Table 4.

Table 4. NIRS devices and sensors.

NIRS devices	Sensors
INVOS oximeter[a]	Small adult SomaSensor (SAFB-SM) (standard) Pediatric SomaSensor (SPFB) OxyAlert Neonatal Sensor (CNN)
Fore-Sight oximeter[b]	Neonatal Sensor (Small Sensor)
Equanox model 7600[c]	Adult Sensor (Classic Sensor 8000 CA)

[a] INVOS 5100C (Covideon). [b] Fore-Sight (CAS Medical Systems Inc).
[c] Equanox model 7600 (NONIN Medical Inc). NIRS: near-infrared spectroscopy.

Study design

Five different NIRS sensors from the three NIRS devices were compared (Figure 4). Two sensors at the time were applied to the frontoparietal part of the head of the neonate, one on each side symmetrically. Sensors were fixated with an opaque elastic bandage to shield the optodes from ambient light. After a period of at least 1 h, sensors were switched to the contralateral side to collect two periods of 60 min of a stable clinical episode, without interference due to, for example, feeding or care. The INVOS (Covidien) adult sensor was used as reference measurement. However, in the course of this research, a practical limitation occurred in comparing the Equanox sensor to the INVOS (Covidien) adult sensor. Strong interference between the two sensors resulted in unreliable results. We therefore adjusted the study design and compared the Equanox sensor with the Fore-Sight neonatal sensor, where the interference problem did not occur. The resulting combinations were as follows:

- INVOS (Covidien) adult sensor (SomaSensor SAFB-SM) vs. INVOS (Covidien) neonatal sensor (Oxyalert CNN)
- INVOS (Covidien) adult sensor (SomaSensor SAFB-SM) vs. INVOS (Covidien) Somanetics pediatric sensor (SomaSensor SPFB)
- INVOS (Covidien) adult sensor ((SomaSensor SAFB-SM) vs. Fore-Sight neonatal sensor (small sensor)
- Equanox sensor (Classic Sensor 8000CA) vs. Fore-Sight neonatal sensor (small sensor)

To correct for the 7% difference between left and right positions, we measured both the devices bilaterally resulting in two measuring periods.[34] Of the 55 included neonates, 10 resulted in only one monitoring period of an hour. In our experience, it usually takes 5 min to produce a reliable signal after application. We therefore did not include the first 5 min into the analysis of the results. Signal Base (a program especially designed at the Wilhelmina Children's Hospital for NIRS signal analysis) was used to convert and to analyze the obtained $rScO_2$ signals.

Statistical analysis

Data were summarized as mean values ± SD or as median values and ranges where appropriate. Simple linear regression analysis was used to analyze the correlation between the different obtained $rScO_2$ signals. Bland–Altman statistics compares the difference between the signals with the average $rScO_2$.[35] Representative $rScO_2$ signals were converted in median values with a sampling rate of one value per minute, because the different NIRS devices use different sampling rates and to exclude the influence of '0'-values (ar-

tifacts). Sixty successive values of each sensor (and if representative of both sides) were analyzed with the Signal Base program. No signals were removed or given less weight during the calculations. We used SPSS 17.0 (SPSS, Chicago, IL) for statistical analysis.

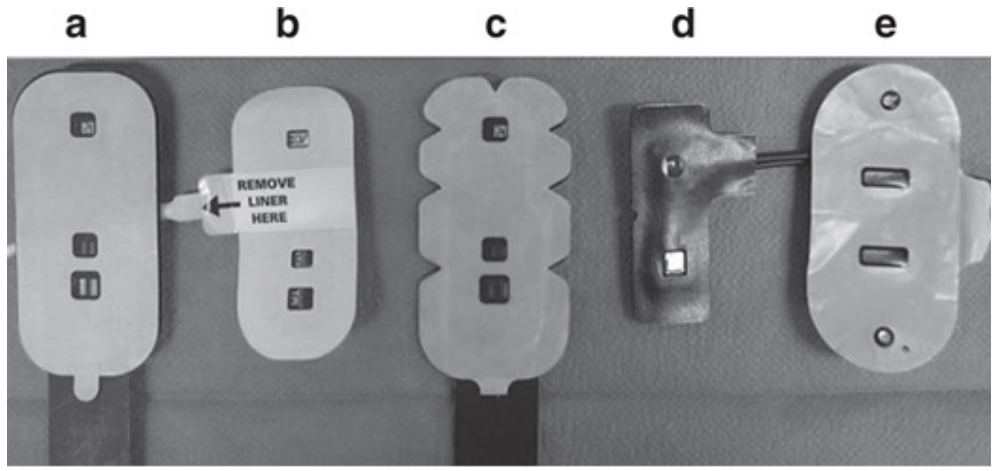

Figure 4. The different NIRS sensors used for comparison. (a) INVOS adult sensor (SomaSensor SAFB-SM) (Covidien). (b) INVOS neonatal sensor (Oxyalert CNN) (Covidien). (c) INVOS pediatric sensor (SomaSensor SPFB) (Covidien). (d) Fore-Sight neonatal sensor (small sensor) (CAS Medical Systems). (e) Equanox sensor (Classic Sensor 8000CA) (NONIN Medical).

Results

Clinical characteristics of all the included infants are shown in Table 1. During the actual data collection, all infants were hemodynamically stable, had normal blood gasses, and were not disturbed by feeding or changing. $rScO_2$ signals were measured in 67 neonates bilaterally. Of these, 55 provided reliable and representative $rScO_2$ signals. Figure 1 shows the simple regression plots of NIRS-monitored $rScO_2$ as a function of comparing two different devices. Figure 2 shows the Bland–Altman plots with the limits of agreement between the two $rScO_2$ signals analyzed per measuring value. Statistical analysis was performed and described per infant. An example is shown in Figure 3. Detailed results are given in the following sections.

Sixteen neonates were monitored with the adult sensor and the neonatal sensor of the INVOS 5100C (Covidien, Troy, MI). Of these, 13 resulted in two measuring periods of 1 h each and 3 in only one measuring period of 1 h. Mean $rScO_2$ was 76 ± 7% for the neonatal

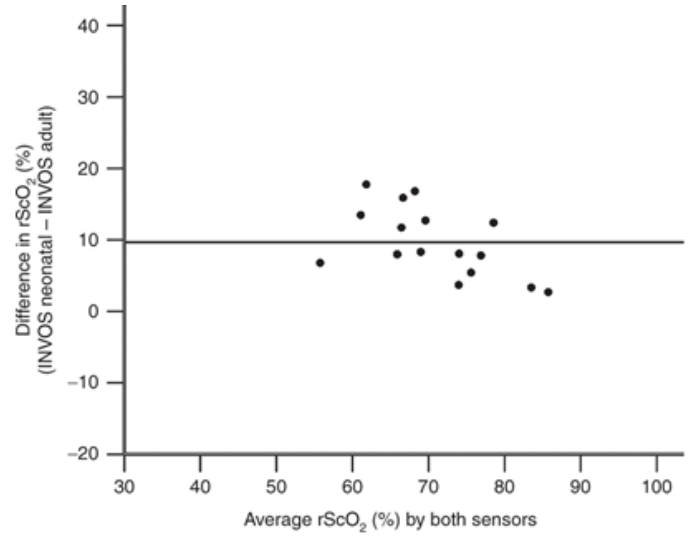

Figure 3. Bland–Altman plot of the near-infrared spectroscopy (NIRS) monitored regional cerebral oxygenation ($rScO_2$) analyzed per infant. The black line in the figure represents the average difference of the $rScO_2$ monitored with the INVOS adult sensor (SomaSensor SAFB-SM) and INVOS neonatal sensor (Oxyalert CNN) (both by Covidien). Average difference, 10 ± 5; limits of agreement, 0–20%.

sensor, and 66 ± 10% for the adult sensor. These means differ significantly ($P < 0.001$). There appeared a close correlation between the two sensors ($r = 0.88$, $P < 0.001$) (Figure 1a). Bland–Altman analysis revealed an average difference of 10 ± 5%. The corresponding limits of agreements are 0–20% (Figure 2a, represented as per measuring value).

In comparing the pediatric sensor with the adult sensor, both from the INVOS 5100C (Covidien), 14 infants were NIRS measured. One infant resulted in only one measuring period of 1 h. Mean $rScO_2$ was 80 ± 10% for the pediatric sensor, and 70 ± 11% for the adult sensor ($P < 0.001$). Linear regression showed a correlation coefficient of $r = 0.89$, $P < 0.001$ (Figure 1b). The Bland–Altman plot shows an average difference of 10 ± 5%. Limits of agreement are 0–20% (Figure 2b, represented as per measuring value). The neonatal sensor of the Fore-Sight device (CAS Medical Systems, Branford, CT) was compared with the adult sensor of the INVOS 5100C (Covidien) in 14 infants. In three infants, measurements resulted in only one measuring period of 1 h. Mean $rScO_2$ was 81 ± 5% for the Fore-Sight neonatal sensor and 66 ± 8% for the INVOS (Covidien) adult sensor ($P < 0.001$). The linear regression coefficient was $r = 0.74$ ($P = 0.002$) (Figure 1c). The average difference was 16 ± 6% and limits of agreement were 4–27% (Figure 2c; represented as per measuring value).

3

Table 1. Patient characteristics.

Sensors	INVOS neonatal[a] — INVOS adult[a]	INVOS pediatric[a] — INVOS adult[a]	Fore-Sight neonatal[b] — INVOS adult[a]	Fore-Sight neonatal[b] — Equanox adult[c]
Total N	16	14	14	11
Male / Female	5 / 11	5 / 9	5 / 9	6 / 5
BW (g) mean ± SD	1330 ± 790	2104 ± 1106	1214 ± 317	1683 ± 983
GA (wk) mean ± SD	30 ± 3	33 ± 5	29 ± 2	31 ± 4
APGAR 5 min; median (range)	7 (1 - 10)	9 (7 - 10)	8 (3 - 10)	9 (3 – 10)
Postnatal age (d) median (range)	2 (1-16)	3 (0-31)	2 (1-15)	4 (0-19)
Respiratory support (n)				
• Non	1	5	1	3
• NF	1	3	3	4
• CPAP	8	2	5	2
• SIMV	6	4	5	2
SGA yes / no	0 / 16	0 / 14	0 / 14	1 / 10

[a] INVOS 5100C (Covideon). [b] Fore-Sight (CAS Medical Systems Inc). [c] Equanox model 7600 (NONIN Medical Inc). BW, birth weight; CPAP, continuous positive airway pressure; GA, gestational age; NF, nasal flow 0.5 l/min; SGA, small for gestational age (<p10); SIMV, synchronized intermittent mandatory ventilation.

The last comparison was between the Equanox (NONIN Medical, Plymouth, MN) sensor and the Fore-Sight neonatal sensor. Eleven neonates were measured, of whom three resulted in one measuring period of 1 h and eight in two measuring periods. Mean $rScO_2$ values were 78 ± 6% for the Fore-Sight neonatal sensor and 65 ± 5% for the Equanox sensor ($P < 0.001$). Linear regression coefficient (r) was 0.62 ($P = 0.054$) showing a similar pattern of differences with the Fore-Sight and INVOS (Covidien) comparisons (Figure 1d). The average difference between the Equanox and Fore-Sight sensors was 15 ± 4% with limits of agreement of 7–23% (Figure 2d; represented as per measuring value). The linear regression analysis and Bland–Altman analysis are summarized in Tables 2 and 3, respectively.

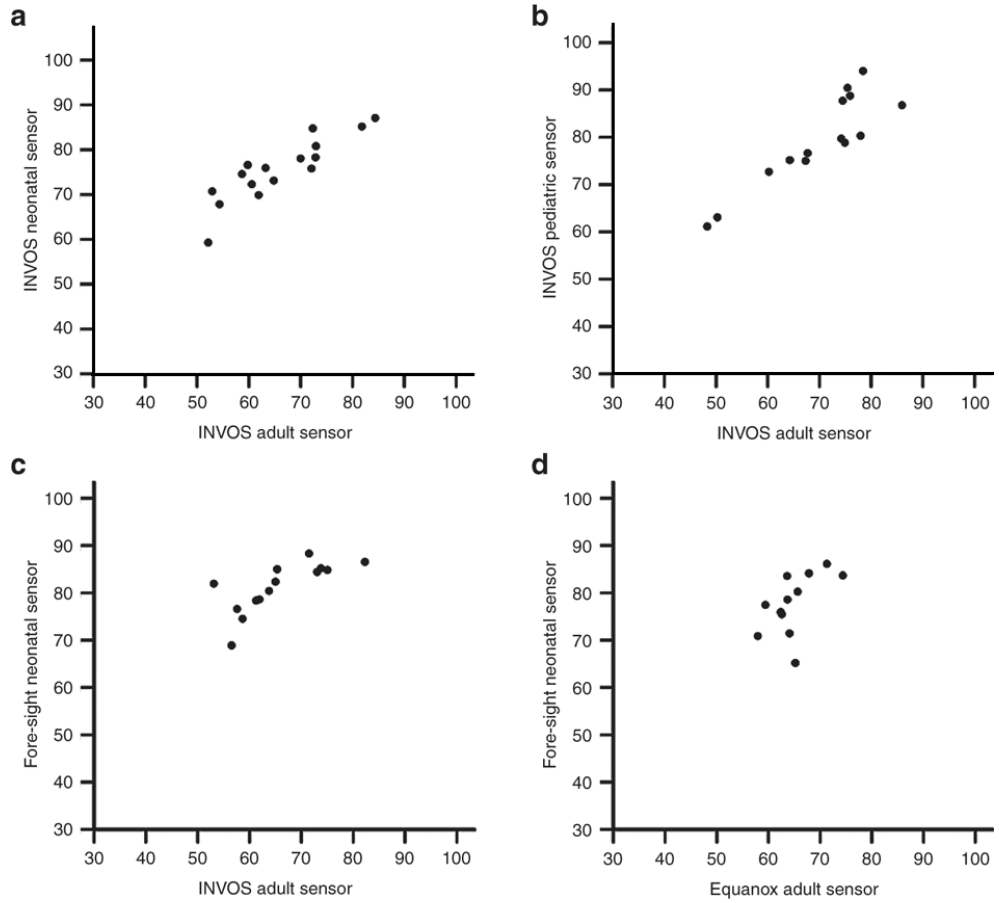

Figure 1. Simple regression plots of the near-infrared monitored regional cerebral oxygen saturation ($rScO_2$) combinations. (a) INVOS adult sensor (SomaSensor SAFB-SM) vs. INVOS neonatal sensor (Oxyalert CNN) (both by Covidien) ($r = 0.88$; $P < 0.001$). (b) INVOS adult sensor (SomaSensor SAFB-SM) vs. INVOS pediatric sensor (SomaSensor SPFB) (both by Covidien) ($r = 0.98$; $P < 0.001$). (c) INVOS adult sensor (SomaSensor SAFB-SM) (Covidien) vs. Fore-Sight neonatal sensor (small sensor) (CAS Medical Systems) ($r = 0.74$; $P = 0.002$). (d) Equanox sensor (Classic Sensor 8000CA) (NONIN Medical) vs. Fore-Sight neonatal sensor (small sensor) (CAS Medical Systems) ($r = 0.57$; $P = 0.054$).

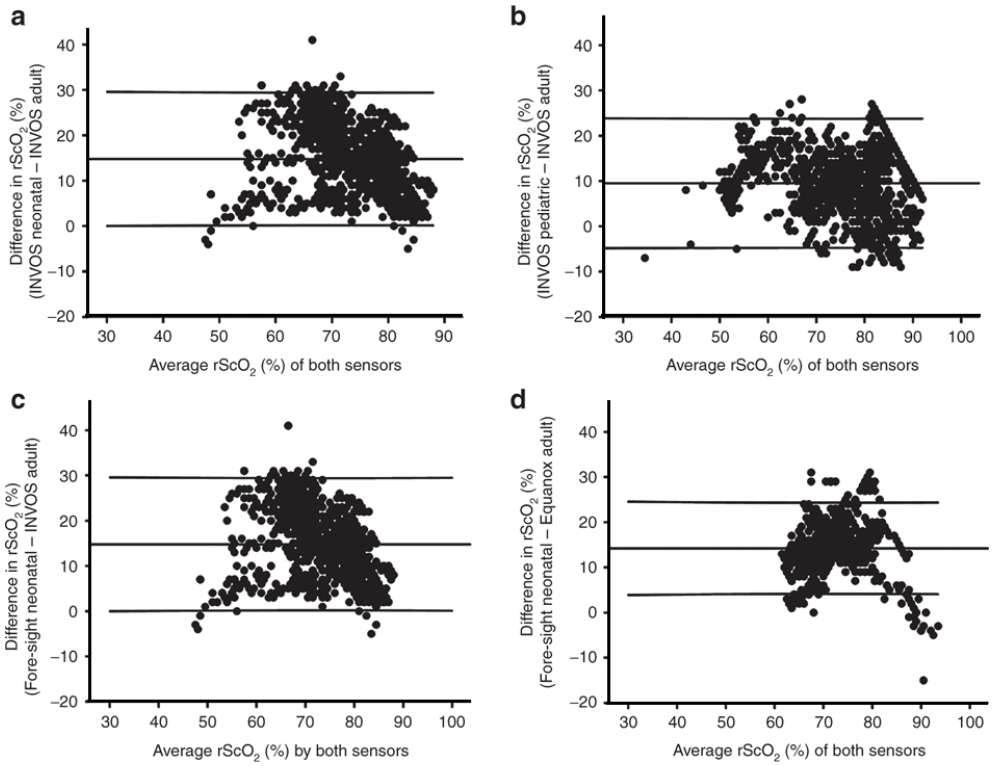

Figure 2. Bland–Altman plots of the near-infrared spectroscopy (NIRS) monitored regional cerebral oxygen saturation ($rScO_2$) combinations (depicted as per-measuring values). The black lines represent the lower and upper limits of agreement and the average difference. (a) INVOS adult sensor (SomaSensor SAFB-SM) and INVOS neonatal sensor (Oxyalert CNN) (both by Covidien), average difference 10 ± 7%; limits of agreement -4 to 24%. (b) INVOS adult sensor (SomaSensor SAFB-SM) vs. INVOS pediatric sensor (SomaSensor SPFB) (both by Covidien), average difference 10 ± 7%; limits of agreement -5 to 24%. The straight line on the right side of panel b indicates the upper limit of the INVOS (Covidien) device. As values become higher, the difference between the two sensors cannot increase along because of the upper limit of 95% installed by the manufacturer. (c) INVOS adult sensor (SomaSensor SAFB-SM) (Covidien) and Fore-Sight neonatal sensor (small sensor) (CAS Medical Systems), average difference 15 ± 7%; limits of agreement 0–30%. (d) Equanox sensor (Classic Sensor 8000CA) (NONIN Medical Inc) and Fore-Sight neonatal sensor (small sensor) (CAS Medical Systems Inc), average difference 14 ± 5%; limits of agreement 4–25%.

Table 2. Linear regression analysis.

Sensors	INVOS adult[a]	INVOS neonatal[a]	INVOS pediatric[a]	Fore-Sight neonatal[b]	Equanox adult[c]
N		16	14	14	11
$rScO_2$, %; mean ± SD	66 ± 10	76 ± 7 P<0.001			
	70 ± 11		80 ± 10 P<0.001		
	66 ± 8			81 ± 5 P<0.001	
				78 ± 6	65 ± 5 P<0.001
Correlation coefficient		r = 0.88 p<0.001	r = 0.89 p<0.001	r = 0.74 p:0.002	r = 0.57 p:0.054

[a] INVOS 5100C (Covideon). [b] Fore-Sight (CAS Medical Systems Inc).
[c] Equanox model 7600 (NONIN Medical Inc).

Table 3. Bland-Altman analysis.

Sensors	INVOS neonatal[a] — INVOS adult[a]	INVOS pediatric[a] — INVOS adult[a]	Fore-Sight neonatal[b] — INVOS adult[a]	Fore-Sight neonatal[b] — Equanox adult[c]
Total N	16	14	14	11
Differences (%) mean ± SD	10 ± 5	10 ± 5	16 ± 6	15 ± 4
Limits of agreement (%)	0 - 20	0 - 20	4 - 27	7 – 23

[a] INVOS 5100C (Covideon). [b] Fore-Sight (CAS Medical Systems Inc).
[c] Equanox model 7600 (NONIN Medical Inc).

Discussion

This study shows a substantial difference in $rScO_2$ between the adult NIRS sensors, irrespective of the brand of the NIRS device on the one hand and the pediatric and neonatal sensors of the two devices on the other hand. The pediatric and neonatal sensors measure consequently higher $rScO_2$ values, ranging from 10 to 16%. The $rScO_2$ values determined with the adult sensors from the INVOS 5100C (Covidien) and the Equanox 7600 devices were comparable although no direct comparison was possible here because of interference of the NIRS signals. Moreover, the $rScO_2$ values obtained with the two neonatal sensors and the pediatric sensor from INVOS (Covidien) provided us with comparable results.

These results are important for clinical practice because the clinician must be able to rely on NIRS-determined cerebral oxygenation using $rScO_2$. The clinical application of NIRS is especially important in detecting hypoxia for preventing hypoxic damage in the neonatal brain. Earlier experimental and human studies in neonatal animals (1- to 3-day-old piglets) and term neonates, respectively, almost always performed with the older (adult) sensors showed that $rScO_2$ values <35–44% for at least 30–60 min lead to functional and/or anatomical hypoxic brain damage.[21-23] The new information gathered in this study strongly suggest that the lower limit of acceptable $rScO_2$ values obtained with the neonatal sensors, irrespective which NIRS device has been used, will be higher. Likewise, the upper limit of $rScO_2$ values to avoid hyperoxia will be different when using the neonatal sensors of the NIRS devices investigated. Important to state here is that this issue has not yet been well investigated at all. In our neonatal intensive care unit (NICU) where we routinely monitor all preterm neonates below 30 weeks of gestation for the first 3 days of life during the last 5 years with the small adult sensor of the INVOS 5100C (Covidien), we use an upper limit 85% being two standard deviations above the expected mean value ±1 SD (71±7%). We obtained these data from a population of ~500 babies (unpublished data), which is well in line with normative data of another study in preterm infants investigated with NIRS devices using adult sensors.[8,12] Hyperoxia has been suspected to be toxic and to negatively influence long-term cognitive and motor outcome of especially the extremely preterm neonates born before 28 wk of gestation.[24] A complicating factor here is that the neonatal sensors of INVOS (Covidien) and Fore-Sight do not measure $rScO_2$ values above 90% as measured with the adult sensors: as can be seen in Figures 2a–d, the values of the pediatric and neonatal sensors of INVOS (Covidien) cannot exceed 95% (upper limit installed by manufacturer) when the adult sensors are still within range of 85–95%. This makes it impossible to rely on these measurements in case of assumed hyperoxia and greatly impair the use of neonatal and pediatric sensors in NIRS-monitored $rScO_2$ in clinical practice. We, therefore, continue using the original adult sensors in our extremely preterm babies, where we have a lot of experience with and an abundant amount of data, until the reason(s) for the discrepancy between adult and pediatric/neonatal sensors with respect to $rScO_2$ values has been solved.

We can only speculate about the reason for the discrepancy in $rScO_2$ values between the different types of NIRS sensors. As we already stated in an earlier report, we postulated that the differences between adult and neonatal sensors are related to differences in the processing of the received NIRS signal. According to the manufacturer of the INVOS 5100C (Covidien) device, for instance, the neonatal sensor has been engineered to have a higher sensitivity. The algorithm for this neonatal sensor has indeed been adjusted to increased signal intensities transmitted through the thinner infant's skull.[20] This makes it easier for the ambient light to enter, and may account for the 10–14% higher values of $rScO_2$ we found in this study, although it may be expected that the instrument will adjust for different light intensities. It is furthermore important to realize that the NIRS devices present in this study use different measurement techniques of $rScO_2$, spatially resolved spectroscopy, and the principles of the Beer–Lambert law to measure cerebral oxygen saturation. Although interference between the two sensors (left and right frontoparietal positions) may account for the higher $rScO_2$ values, this does not seem very likely because the preamplifier and the distance between the NIRS sensors actually prevent this interference. Other differences in technical details, low hemoglobin values (not the case in our investigated group, data not shown), or extra cranial blood flow could contribute to the differences between sensors but are not very probable. Differences in intracranial blood flow could account for differences between the two sides of the neonatal head. We tried to compensate for differences between left and right positions by measuring both the sides with the two sensors. Earlier studies have shown that differences are usually within the range of 7%; recent work compared the neonatal sensor and found even higher differences between left and right positions.[20] Finally, as the sensors are of different sizes and use different wavelengths, the size of the measured area and signal depth could be uneven. Although beyond the scope of this study, other reasons for differences between $rScO_2$ values measured in extremely preterm infants can be manifold. Besides differences in the techniques as stated above, differences in postmenstrual and postnatal age[25-28] or differences induced by the different locations of the brain under investigation[29] may contribute to differences in $rScO_2$. It will be worthwhile and clinically very important to further investigate these issues in relation to cerebral oxygen saturation.

The main disadvantage of the adult sensors as compared with the smaller pediatric or neonatal sensors is its size. Intensive neonatal care is often extensive including the need for repeated cranial ultrasound investigations, monitoring of the electrical brain activity with amplitude-integrated electroencephalogram, and the need for artificial ventilation.

Considering how small a neonatal head can be in these extremely preterm babies, smaller NIRS sensors could surely be of advantage; but only when their technical details are fully known and reliable, $rScO_2$ values can be measured.

Further research should therefore focus on whether it is possible to correct for the differences between the different types and brands of commercially available sensors. This issue is particularly pressing, given the fact that recent (although preliminary) research suggests that $rScO_2$ values are indeed higher in the (preterm) neonate and were reported to be between 79 and 85%.[30]

Conclusion

In summary, we conclude that there appears to be a good correlation between the different NIRS sensors used in the NICU. However, differences between $rScO_2$ values measured with the adult sensor and the pediatric and neonatal sensors range between 10 and 16%, being higher in the pediatric and neonatal sensors.

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Reference values of regional cerebral oxygen saturation during the first 3 days of life in preterm neonates

4

Thomas Alderliesten[1], Laura M. L. Dix[1]
Willem Baerts[1], Alexander Caicedo Dorado[2,3]
Sabine van Huffel[2,3], Gunnar Naulaers[4]
Floris Groenendaal[1], Frank van Bel[1]
Petra M. A. Lemmers[1]

[1] Department of Neonatology, Wilhelmina Children's Hospital,
University Medical Center Utrecht, Utrecht, The Netherlands
[2] Department of Electrical Engineering (ESAT), Division SCD KU Leuven, Leuven, Belgium
[3] iMinds-KU Leuven Future Health Department, Leuven, Belgium
[4] Department of Neonatology, University Hospital The Gasthuisberg, Leuven, Belgium

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CHAPTER 4

Reference values of regional cerebral oxygen saturation during the first 3 days of life in preterm neonates

Abstract

Background Currently, reliable reference values of regional cerebral oxygen saturation ($rScO_2$) for different gestational age (GA) groups are lacking, which hampers the implementation of near-infrared spectroscopy (NIRS) alongside monitoring arterial oxygen saturation (SaO_2) and blood pressure in neonatal intensive care. The aim of this study was to provide reference values for $rScO_2$ and cerebral fractional tissue oxygen extraction (cFTOE; $(SaO_2 - rScO_2)/SaO_2$) for small adult and neonatal NIRS sensors.

Methods In this study, 999 infants born preterm (GA <32 wk) were monitored with NIRS during the first 72 h of life. Mixed modeling was used to generate reference curves grouped per 2 wk of GA. In addition, the influence of a hemodynamically significant patent ductus arteriosus, gender, and birth weight were explored.

Results Average $rScO_2$ was ~65% at admission, increased with GA (1% per week) and followed a parabolic curve in relation to postnatal age with a peak at ~36 h. The cFTOE showed similar but inverse effects. On average, the neonatal sensor measured 10% higher than the adult sensor.

Conclusion $rScO_2$ and cFTOE reference curves are provided for the first 72 h of life in preterm infants, which might support the broader implementation of NIRS in neonatal intensive care.

Introduction

Despite advances in neonatal intensive care that have led to a decline in morbidity, preterm birth is still associated with neurological sequelae.[1] Brain injury in preterm infants is often caused by disturbances in cerebral blood flow (CBF) and oxygenation.[2-4] Evidence is accumulating that monitoring blood pressure alone is not enough to ensure adequate (cerebral) perfusion and oxygenation.[5,6]

Near-infrared spectroscopy (NIRS) is a technique that can be used to monitor regional cerebral oxygen saturation ($rScO_2$), being both a measure of cerebral oxygenation as well as a surrogate of CBF. NIRS monitoring can be applied for prolonged periods of time, even in the most vulnerable infants.[7] It uses multiple wavelengths of NIR light and relies on the distinct absorption spectra of oxygenated (O_2Hb) and deoxygenated (HHb) hemoglobin to calculate relative concentrations of O_2Hb and HHb, which are then used to calculate the $rScO_2$ ($O_2Hb/(O_2Hb + HHb)$). Where pulse-oximetry only measures the oxygen saturation in arterial blood (SaO_2), NIRS makes no distinction between different (cerebral) blood volume compartments; therefore, the $rScO_2$ represents the oxygen saturation in a mixed arterial–capillary–venous compartment in an approximate 20:5:75 distribution.[8]

NIRS is increasingly being used as a trend monitor of cerebral oxygen supply in neonates admitted to the neonatal intensive care unit (NICU). Readily interpretable reference values could provide another way of using NIRS in neonates by identifying neonates at risk. In other words, to identify neonates whose $rScO_2$ resides at the outskirts (high or low) of what is considered "normal." Furthermore, reliable reference values could benefit NIRS research by suggesting thresholds that should be explored in relation to interventions and (neurodevelopmental) outcome. However, current literature is quite heterogeneous, with different age groups, small sample sizes, different onsets and durations of measurement, and the use of different devices and sensors.[9–15] Therefore, the aim of this study was to construct gestational age (GA)–specific reference curves during the first 72 h of life for $rScO_2$ and its derived cerebral fractional tissue oxygen extraction (cFTOE ($SaO_2 - rScO_2$)/SaO_2) in a large group of neonates who were measured with a small adult NIRS sensor (SomaSensor SAFB-SM using INVOS 4100 or 5100c monitors).[16] The second aim was to provide a conversion model to convert $rScO_2$ values obtained by a neonatal sensor (OxyAlert CNN cerebral NIRsensor; Covidien) to the adult sensor equivalent.

Methods

Patients

This study is part of an ongoing prospective observational cohort study which aims to record physiological parameters during at least the first 72 h of life in all infants born with a GA <32 wk who are admitted to the NICU of the Wilhelmina Children's Hospital, Utrecht, The Netherlands. The medical ethical board of the University Medical Center Utrecht approved this study. Informed parental consent was obtained in all cases. Data collection was attempted in 1,059 infants between January 2005 and September 2013.

Data collection

Obstetrical, intrapartum, and neonatal data were collected from the hospital records. Peri- and intra-ventricular hemorrhages (PIVH) were graded according to the classification of Papile et al.[34] The presence of a hsPDA was defined as a PDA confirmed to be hemodynamically significant on cardiac ultrasound and either treated with indomethacin or surgically closed.[2]

Standard physiological parameters were monitored using a patient monitor (IntelliVue MP70, Philips, Best, The Netherlands): SaO_2 using a pulse-oximetry probe, arterial blood pressure by means of an indwelling catheter (e.g., umbilical, radial, or tibial artery), and heart rate by gel electrodes. In general, the pulse-oximetry probe was placed on one of the lower limbs. In case of a hsPDA, the probe was placed on the right hand (i.e., preductal). $rScO_2$ was monitored by using a two-wavelength (i.e., 730 and 810 nm) NIRS monitor (INVOS 4100 or 5100(c)); Covidien, Mansfield, MA) in combination with a small adult sensor (SomaSensor SAFB-SM, Covidien). An elastic bandage was used for sensor fixation. Until June 2012, data were recorded with Poly 5 (Inspector Research Systems, Amsterdam, The Netherlands) at a sample rate of 1 Hz using an INVOS 4100 monitor. Thereafter, in-house developed software (BedBase, University Medical Center Utrecht, Utrecht, The Netherlands) was used to record data from the patient monitor and an INVOS 5100c NIRS monitor at a sample rate of 0.4 Hz.

Data processing

Data were analyzed with the offline version of the BedBase software (SignalBase, University Medical Center Utrecht, Utrecht, The Netherlands). Before analysis, artifacts were removed manually. Artifacts were defined as: changes in $rScO_2$ that could not be physiologically explained (e.g., a 30% step change between two subsequent data points) or

changes that were accompanied by severe distortion in the other parameters suggesting infant movement or handling. Thereafter, 1-h periods were selected during the first 72 h of life and counted in reference to a patient's birth date and time (i.e., PA). Periods with short drops in SaO_2 (i.e., <85%) were not included in the analysis. In case of SaO_2 drops where additional O_2 was given to assist recovery, the duration of the associated increase in SaO_2 and $rScO_2$ over baseline conditions was also excluded from analysis.[35]

Statistical analysis

Before statistical analysis, 1-h periods containing less than 10 min of data were rejected. Mean values of the 1-h periods were used for analysis. A mixed-model approach was performed using R for Windows 64-bit, version 3.1.1 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) with the nlme package. This approach can handle missing data and obsoletes correcting for multiple comparisons. The decision was made, a priori, to investigate four variables: GA (in weeks), BW z-score, gender, and the presence of a hsPDA. The BW z-score was based on recently published Dutch reference curves and explored both as a continuous variable and dichotomized at –1 SD and –2 SD.[36] The time of diagnosis of a hsPDA was expressed as PA at time of the cardiac ultrasound. This PA at diagnosis was dichotomized at different cutoffs, ranging from 60 to 132 h with 12-h increments.

Linear, squared, and polynomial models of time (i.e., PA) were explored to find the best fit to the data. Either the $rScO_2$ or cFTOE was selected as the dependent variable, with the individual subject as a random factor. Both main effects and interactions with PA were explored. It was decided a priori that interactions with PA would be included into the final model when the interaction was statistically significant and caused at least a 10% coefficient change with respect to the coefficient for PA in the model with only main effects.

The final model was used to create $rScO_2$ and cFTOE reference curves by generating predictions based on a new set of predictors (i.e., PA, GA, hsPDA, gender, and BW). This new set was generated as follows: PA ranging 1–72 h with 0.2-h increments (e.g., 1.0, 1.2, 1.4 h, etc.), GA ranging 24–32 with 1-wk increments, hsPDA yes/no, female gender yes/no, and BW <–1 SD yes/no. The SEs of these predictions were calculated and used to create percentile plots based on a normal distribution. To assess the robustness of the results, analysis was also performed using GAMLSS in R with the GAMLSS package.[37] Unless specified otherwise, data are presented as mean with SD for parametric data, median with interquartile range for nonparametric data, and counts (%) for categorical data. A P value < 0.05 was considered statistically significant.

Conversion models for neonatal NIRS sensor

In a subset of infants (n = 16, GA 30 ± 3 wk), $rScO_2$ was recorded bilateral by using the neonatal (OxyAlert CNN cerebral NIRsensor) and small adult sensor (SAFB-SM, as described above), as reported previously.[14] Both sensors use a single LED light source, two distant detectors (30 and 40 mm), and two wavelengths (i.e., 730 and 810 nm). After at least 1 h of stable recordings (e.g., free of care, feedings, and interventions), the sensors were switched to the contralateral side, and data collection continued for another hour. Data analysis was performed in MATLAB (vR2011b; The Mathworks, Natick, MA), and artifacts were removed manually. A linear model, polynomial models, and a piecewise linear model were examined to find the best fit (i.e., lowest residuals and highest R2) in order to convert data obtained by the neonatal sensor to small adult sensor–equivalent values and *vice versa*.

Results

Out of the 1,059 participating infants, 41 were excluded because of technical problems during data collection (e.g., data corruption, missing cable connections, or electrical interference). An additional 19 infants were excluded for having cardiac malformations (n=8), chromosomal or severe genetic abnormalities (n=6), or severe congenital malformations (n=5). Table 1 summarizes the clinical characteristics of the study population.

A total of 59,135 1-h periods (median: 873; interquartile range: 817–905 per 1-h period) were available for analysis. Although 1-h periods were used for modeling, Figure 1 displays the raw $rScO_2$ and cFTOE data in 6-h averages for the first 24 h and 12-h averages for the 48 h thereafter to yield an easily interpretable figure.

Figures 2 and 3 display the main results: the $rScO_2$ and cFTOE reference curves for four different GA groups. Depending on GA and postnatal age (PA), the mean $rScO_2$ during the first 72 h of life ranges from 62 to 71%, with a positive association between $rScO_2$ and GA. A single SD in $rScO_2$ is ~7%, which provides a ±2 SD bandwidth of ~30%. Likewise, mean cFTOE ranges from 0.25 to 0.34 during the first 72 h of life, and a single SD is 0.08, which provides a ±2 SD bandwidth of 0.32.

Table 1. Clinical characteristics

	Total	24-25 wk	26-27 wk	28-29 wk	30-31 wk
Male / female, n	539 / 460	57 / 50	128 / 111	171 / 143	183 / 156
Gestational age (weeks), mean (SD)	28.7 (1.96)	25.1 (0.57)	27.0 (0.59)	28.9 (0.57)	30.8 (0.55)
Birth weight (grams), mean (SD)	1150 (330)	770 (110)	930 (180)	1193 (244)	1385 (318)
Birth weight z-score, mean (SD)	0.02 (0.90)	0.40 (0.84)	0.04 (0.83)	0.12 (0.88)	-0.12 (0.91)
Birth weight <1SD, n (%)	142 (14.2)	5 (4.7)	29 (12.1)	40 (12.7)	68 (20.1)
Apgar 1 min, median (IQR)	7 (5-8)	5 (3-6)	6 (4-7)	7 (5-8)	7 (6-8)
Apgar 5 min, median (IQR)	8 (7-9)	7 (6-8)	8 (7-9)	8 (8-9)	9 (8-9)
Head circumference (cm), mean (SD)	26.1 (2.3)	22.8 (1.4)	24.7 (1.6)	26.4 (1.6)	27.8 (1.9)
aCCS full course, n (%)	725 (72.6)	78 (72.9)	172 (72)	236 (75.2)	239 (70.5)
hsPDA, n (%)	294 (29.4)	78 (72.9)	127 (46.9)	75 (23.9)	29 (8.6)
PNA at hsPDA (h), median (IQR)	55 (29-91)	58 (38-113)	59 (28-81)	52 (25-86)	62 (28-82)
PIVH, n (%)					
- None	713 (71.4)	54 (50.5)	156 (65.3)	231 (73.6)	272 (80.2)
- Grade 1	88 (8.8)	6 (5.6)	18 (7.5)	34 (10.8)	30 (8.8)
- Grade 2	110 (11.0)	28 (26.2)	25 (10.5)	35 (11.1)	22 (6.5)
- Grade 3	59 (5.9)	16 (15.0)	32 (13.4)	10 (3.2)	1 (0.3)
- Grade 4	29 (2.9)	3 (2.8)	8 (3.3)	4 (1.3)	14 (4.1)
Hospital mortality, n (%)	65 (6.5)	23 (21.5)	25 (10.5)	13 (4.1)	4 (1.2)
CRIB II score, median (IQR)	9 (7-11)	14 (13-16)	12 (10-13)	8 (7-9)	6 (5-7)

Day	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
Spontaneous breathing, n	535	547	573	20	22	26	69	74	84	188	189	194	258	262	269
%	53.6	54.8	57.5	18.7	20.6	24.3	28.9	31.0	35.4	59.9	60.2	61.8	76.1	77.3	79.4

aCCS: antenatal corticosteroids; CRIB: Clinical Risk Index for Babies; hsPDA: hemodynamically significant Patent Ductus Arteriosus; IQR: Inter-quartile range; PA: postnatal age; PIVH: periventricular/intraventricular hemorrhage; SD: standard deviation

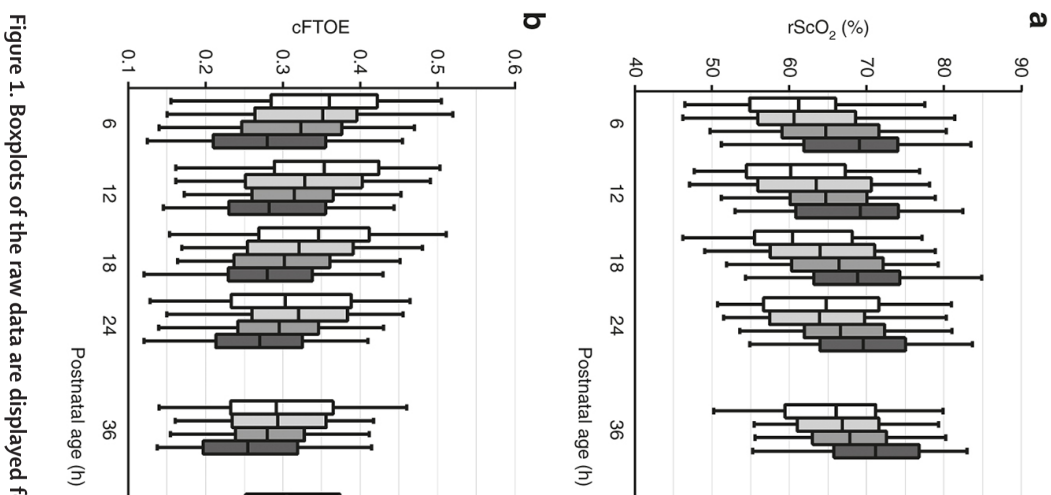

Figure 1. Boxplots of the raw data are displayed for four gestational age groups. White boxes indicate 24–25 wk, light gray boxes indicate 26–27 wk, dark gray boxes indicate 28–29 wk, and black boxes indicate 30–31 wk for (a) regional cerebral oxygen saturation (rScO2) and (b) cerebral fractional tissue oxygen extraction (cFTOE). Data are displayed in 6-h periods for 0–24 h after birth and in 12-h periods for 24–72 h after birth.

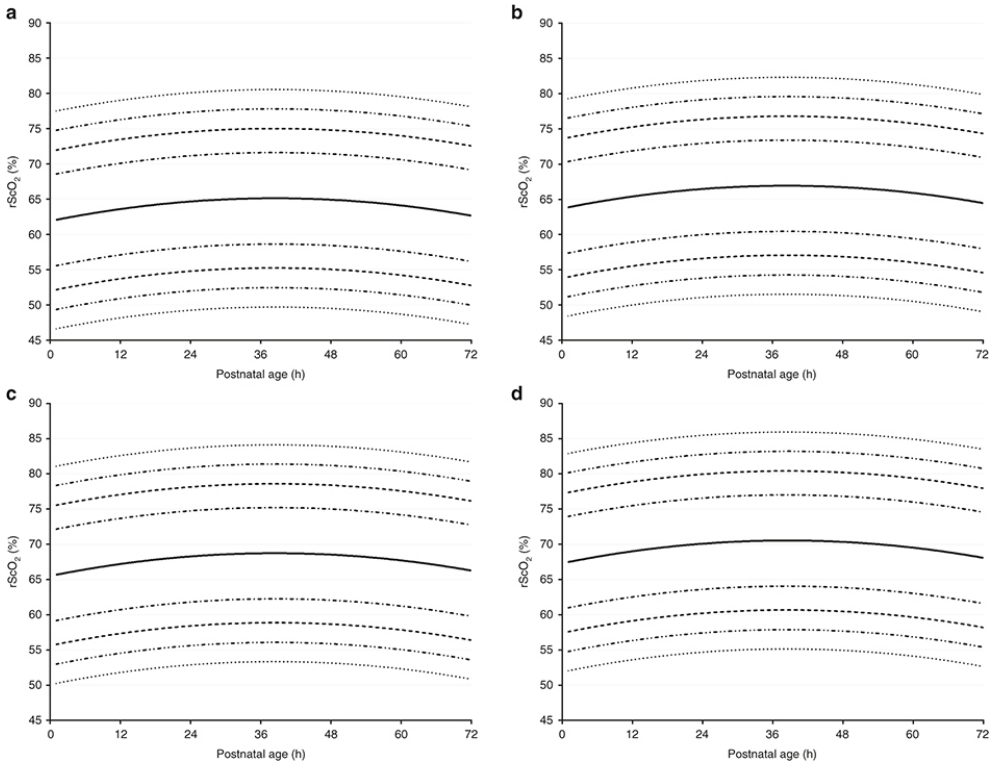

Figure 2. rScO2 reference value curves for neonates. (a) 24–25 wk GA, (b) 26–27 wk GA, (c) 28–29 wk GA, and (d) 30–31 wk GA. The line patterns depict different percentiles: dotted lines indicate p2.3 and p97.7, dash dot dot dash lines indicate p5 and p95, dashed lines indicate p10 and p90, dash dot dash lines indicate p20 and p80, and solid lines indicate p50. GA, gestational age.

Table 2 lists the coefficients of the $rScO_2$ and cFTOE models. For example, mean $rScO_2$ increases 0.9% per week of GA. In the models, PA is also represented by the square of PA (PA-sq) to model the parabolic relationship that $rScO_2$ and cFTOE have with PA. The PA, PA-sq, and interactions with PA and PA-sq determine the location of the vertex (i.e., maximum for rScO2 and minimum for cFTOE) and the curvature of the parabola. Figure 4 is a graphical representation of the main effects and interactions of being born with a birth weight (BW) <–1 SD (i.e., small for gestational age, SGA) and having a hemodynamically significant patent ductus arteriosus (hsPDA) as reported in Table 2.

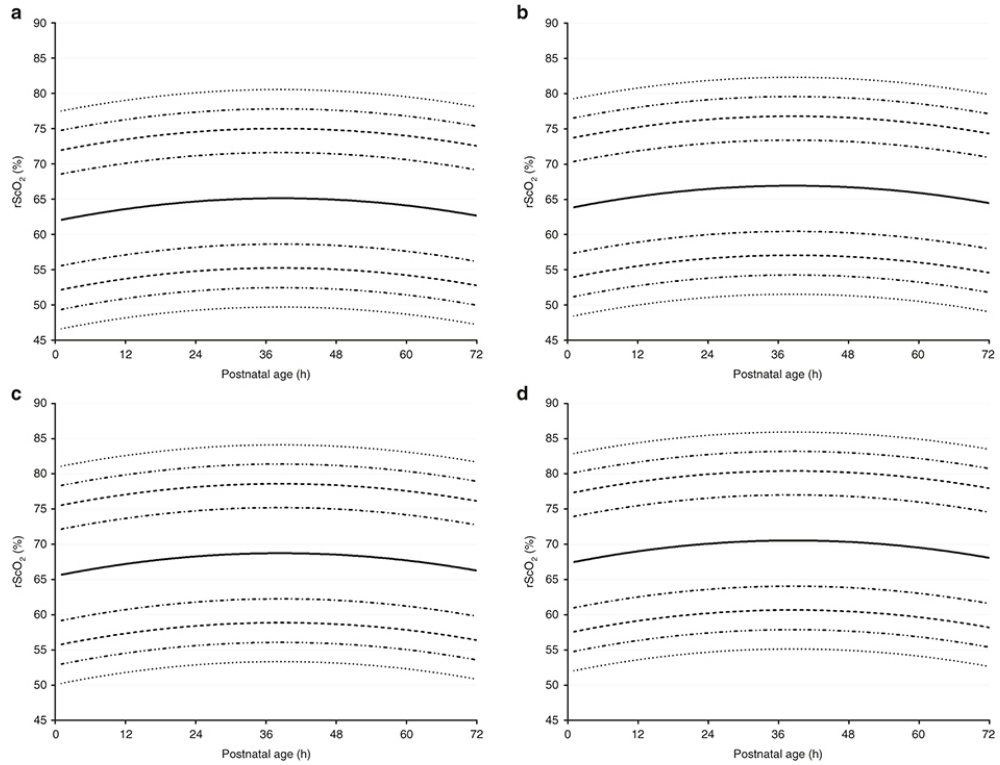

Figure 3. cFTOE reference value curves for neonates. (a) 24–25 wk GA, (b) 26–27 wk GA, (c) 28–29 wk GA, and (d) 30–31 wk GA. The line patterns depict different percentiles: dotted lines indicate p2.3 and p97.7, dash dot dot dash lines indicate p5 and p95, dashed lines indicate p10 and p90, dash dot dash lines indicate p20 and p80, and solid lines indicate p50. GA, gestational age.

Infants who developed a hsPDA <84 h of life had a lower $rScO_2$ and demonstrated a sharper decline after ~24 h. Infants born SGA started off with a higher $rScO_2$ and had slightly lower values at 72 h compared to those at 1 h PA, whereas infants born appropriate for gestational age (AGA) had higher values at 72 h than at 1 h PA. This difference between infants born SGA and those born AGA diminishes over time (i.e., SGA and AGA lines in Figure 4 converge) but is still present at 72 h PA. No significant differences were found between data obtained before or after June 2012 (i.e., Poly 5 software + INVOS 4100 vs. BedBase software + INVOS 5100c).

Table 2. Final model coefficients for the rScO2 and cFTOE.

	$rScO_2$		FTOE	
	Coefficient	95 % CI	Coefficient[c]	95 % CI
Intercept	59.415	58.138; 60.693***	36.033	34.581; 37.486***
Main effects				
• PA (h)	0.240	0.207; 0.273***	-0.221	-0.255; -0.188***
• PA-sq[a]	-0.003	-0.003; -0.002***	0.0023	0.002; 0.003***
• hsPDA≤84h	-0.581	-1.652; 0.490	-0.113	-1.263; 1.036
• GA[b]	0.904	0.699; 1.108***	-0.795	-1.039; 0.552***
• Female gender	-1.565	-2.308; -0.822***	1.729	0.946; 2.512***
• BW≤1SD	6.172	4.371; 7.973***	-3.960	-5.243; -2.677***
Interactions				
• PA: BW≤1SD	-0.1431	-0.2325; -0.0536**	n/a	-
• PA-sq: hsPDA≤84h	-0.00029	-0.00052; -0.00005*	0.00034	0.00007; 0.00061*
• PA-sq: BW≤1SD	0.00014	0.0002; 0.0025*	0.00040	0.00008; 0.00071*
• PA-sq:GA	n/a	-	0.00007	0.00001; 0.00013*

BW, birth weight; CI, confidence interval; GA, gestational age; hsPDA, hemodynamically significant patent ductus arteriosus; n/a, not applicable; PA, postnatal age. [a] PA-sq, postnatal age squared to enable a squared model. [b] GA-24, to make 24 wk of gestation the reference point to yield a interpretable intercept. [c] $(SaO_2 - rScO_2)/SaO_2 \times 100$, to obtain coefficients with the same effect size as for the $rScO_2$. *p<0.05; **p<0.01; ***p<0.001.

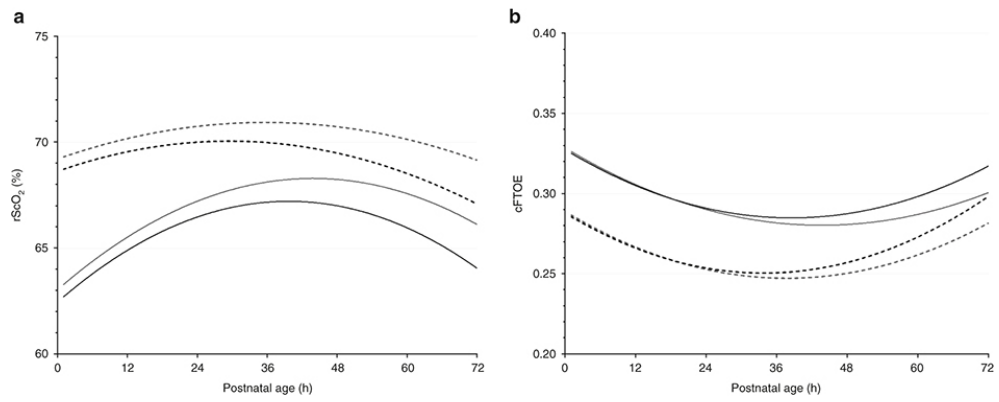

Figure 4. Graphic representation of the interactions of hsPDA and SGA with the representatives of postnatal age in the model for (a) $rScO_2$ and (b) cFTOE. Black solid lines indicate AGA with hsPDA, gray solid lines indicate AGA without hsPDA, black dashed lines indicate SGA with hsPDA, and gray dashed lines indicate SGA without hsPDA. AGA, appropriate for gestational age; cFTOE, cerebral fractional tissue oxygen extraction; hsPDA, hemodynamically significant patent ductus arteriosus; $rScO_2$, regional cerebral oxygen saturation; SGA, small for gestational age.

Conversion diagrams

A strict linear model provided the best fit to convert data obtained by the SAFB-SM (adult) sensor to the CNN (neonatal) sensor: $rScO_{2\text{-neo}} = 0.8481 * rScO_{2\text{-adult}} + 19.11$, $R^2 = 0.65$. Figure 5 is a conversion of Figure 2 by using this equation.

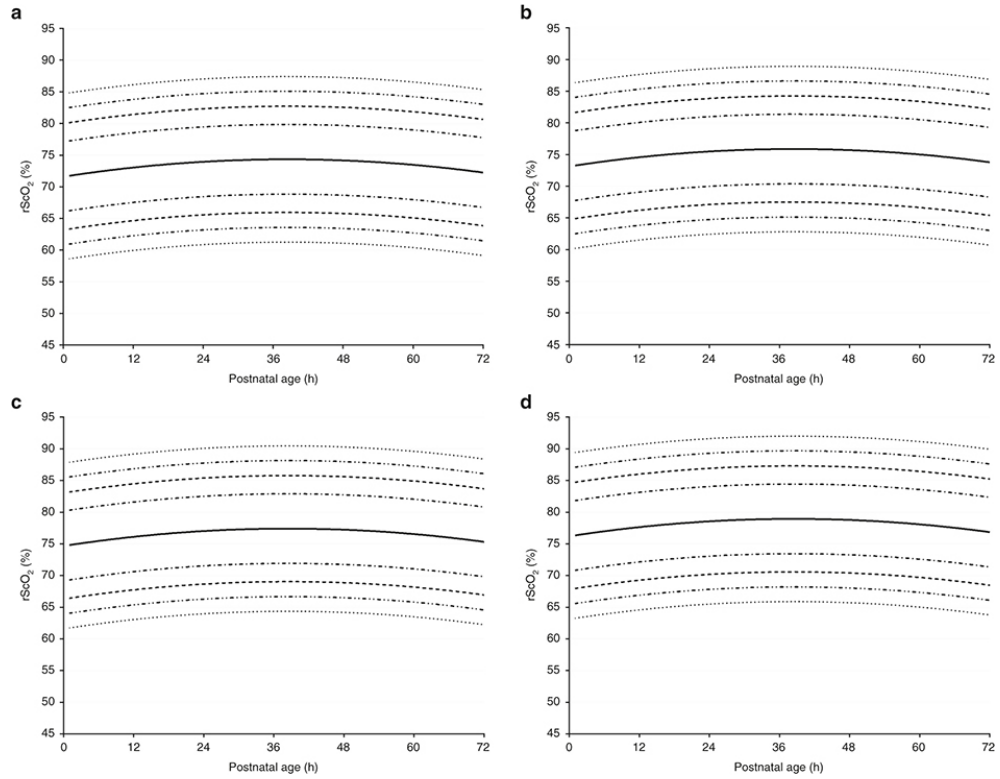

Figure 5. $rScO_2$ reference value curves obtained with the neonatal sensor for neonates. (a) 24–25 wk GA, (b) 26–27 wk GA, (c) 28–29 wk GA, and (d) 30–31 wk GA. The line patterns depict different percentiles: dotted lines indicate p2.3 and p97.7, dash dot dot dash lines indicate p5 and p95, dashed lines indicate p10 and p90, dash dot dash lines indicate p20 and p80, and solid lines indicate p50. Note: the neonatal probe (CNN) rSc02 values were obtained by using a conversion from the adult (SAFB-SM) probe values: $rScO_{2\text{-neo}} = 0.8481\ rScO_{2\text{-adult}} + 19.11$. GA, gestational age; $rScO_2$, regional cerebral oxygen saturation.

Discussion

This is the first study to report reference values of $rScO_2$ and cFTOE obtained using NIRS during the first 72 h of life in a large cohort of preterm neonates born at a GA <32 wk. Four factors should be taken into account when comparing the work reported here to work of others: (i) GA, (ii) PA, (iii) sample size, and (iv) the sensor and device that were used (see discussion below). Values found in the literature agree quite well with the values reported here (Table 3, mean difference: −0.9%). The differences are likely explained by the characteristics of the reported populations (e.g., GA, PA, specific morbidity), duration of measurements, and small sample sizes.[9-11,17-20] It seems likely that the $rScO_2$ will either stabilize or may even increase again after 72 h.[12,13,15,21] Note that van Hoften et al. collected data with a pediatric sensor and Pocivalnik et al. and Pichler et al. with a neonatal sensor.[15,20,21]

It is noteworthy how close the −2 SD bands (i.e., p2.3) are to the $rScO_2$ threshold (i.e., 33–44%) reported to be associated with functional impairment of the brain.[22,23] A lower CBF, either regional or global, in infants with a lower GA is the most plausible explanation for the positive association between GA and $rScO_2$. Roche-Labarbe et al., while using a frequency domain NIRS system, also demonstrated lower levels of cerebral oxygenation during the first 7 wk of life in infants with a GA <31 wk compared to infants with a GA >31 wk.[24] Furthermore, their data show that infants with a GA of 24–27 wk have the lowest blood flow index, supporting lower CBF as an explanation for lower cerebral oxygenation in younger infants. No associations were found between head circumference and $rScO_2$, and SaO_2 and GA. This makes the influence of head circumference (i.e., different curvature of the head influencing NIRS from a technical point of view) or SaO_2 unlikely.

Furthermore, a similar (inverse) association was found between GA and cFTOE. An increased metabolic demand in neonates of lower GA seems unlikely as cerebral activity increases with GA.[25]

Female neonates had lower $rScO_2$ as compared to male neonates. This gender difference was also observed by the Pichler et al. during transition from fetal to neonatal life (personal communication, data not published). Again, this could not be explained by a difference in SaO_2 or head circumference. Therefore, possible explanations are a higher (regional) CBF or lower metabolic demand. A hsPDA can cause a ductal steal phenomenon with a surplus of pulmonary flow at the cost of systemic perfusion and thus CBF.[26] Although notably increasing with PA, the effect of a hsPDA seems rather limited during the first 3 d of life. The most plausible explanation for this is the fact that most hsPDAs become clinically apparent from day 3 onward. In addition, an objectively present

Table 3. $rScO_2$ values obtained from the literature compared to $rScO_2$ reference values established in this study.

	Literature values					Current study		Difference
	Time	Measure	GA (wk)	N	$rScO_2$/TOI (%)	Ref. GA group	$rScO_2$ (%)	Current – literature
0-72h								
Naulaers et al.[9]	Day 1	TOI	28 (25-30)	15	57 (54-66)	28-29 (12h)	67.2	10.2
	Day 2	-	-	-	66 (62-82)	28-29 (36h)	68.7	2.7
	Day 3	-	-	-	76 (68-80)	28-29 (60h)	67.7	-8.3
Lemmers et al.[17]	6-12h	$rScO_2$	29.3 (1.7)	20	70 (61-77)	28-29 (12h)	67.2	-2.8
	18-24h	-	-	-	68 (63-75)	28-29 (24h)	68.3	0.3
	36-48h	-	-	-	73 (65-84)	28-29 (48h)	68.5	4.5
	60-72	-	-	-	71 (64-75)	28-29 (72h)	66.3	-4.7
Sorensen et al.[11]	19h (6)	TOI	27.6 (23.9-33)	37	74.6 (8.5)	26-27 (18h)	66.5	-8.1
Moran et al.[19]	Day 1	TOI	29 (25.3-31.5)	27	68.1 (7.9)	28-29 (12h)	67.2	-0.9
Pichler et al.[20]	<1h	$rScO_2$	34.9 (1.4)	27	80 (62-92)	34-35 (1h)	79.5[ab]	-0.5
Sirc et al.[18]	6h	TOI	25.9 (1.7)	22	65.2 (10)	24-25 (6h)	62.8	-2.4
	12h	-		-	63.9 (5.9)	24-25 (12h)	36.6	-0.3
	24h	-		-	68.8 (5.7)	24-25 (24h)	64.7	-4.1
	48h	-		-	67.2 (7.2)	24-25 (48h)	64.9	-2.3
Hyttel-Sørensen et al.[10]	Average 3 d	$rScO_2$	26.3	10	64.2 (4.5)	26-27 (36h)	66.9	2.7
Average difference								-0.9
>7d of life								
van Hoften et al.[21]	17d (1-93d)	$rScO_2$	27.3 (25-34)	33	71 (65-96)	26-27 (72h)	74.7[b]	3.7
Petrova et al.[12]	>7d	$rScO_2$	(24-32)	20	66 (8.8)	28-29 (72h)	66.3	0.3
Petrova et al.[13]	~5wk	$rScO_2$	26 (2.4)	10	68.5 (4.6)	26-27 (72h)	66.3	-2.2
Pocivalnik et al.[15]	3.9d (4.8)	$rScO_2$	35.2 (3.0)	37	84.1 (6.4)	34-35 (72h)[a]	80.0[ab]	-4.1
	-	TOI	-	-	72.2 (6.0)	34-35 (72h)[a]	71.3[a]	-0.9

GA, gestational age; $rScO_2$, regional cerebral oxygen saturation; TOI, tissue oxygenation index. [a] Model fit was obtained in subjects ≤32 wk GA; therefore, data >32 wk GA was extrapolated. [b] Study used a neonatal sensor; for comparison, the following conversion was used: $rScO_{2\text{-neo}} = 0.8481 \times rScO_{2\text{-adult}} + 19.11$.

hsPDA (i.e., confirmed by cardiac ultrasound) does not necessarily decrease CBF, and thus $rScO_2$, as the magnitude of systemic steal depends on shunt volume and left ventricular output. Moreover, in this study, the PA at diagnosis was dichotomized (i.e., ≤84 h); therefore, the exact PA of the individual at diagnosis and start of treatment was not taken into account. In previous publications, we took a different approach with case–control designs and the start of indomethacin or surgery as time reference, at median postnatal days 2 and 7, respectively.[26,27]

Higher $rScO_2$ values in infants born SGA demonstrate the brain-sparing effect with a compensatory higher CBF. This has been demonstrated previously with other techniques.[28] The difference in $rScO_2$ between SGA and AGA infants diminishes over time, suggesting that the CBF returns to normal after day 3. Interestingly, unlike in AGA infants, $rScO_2$ values in SGA infants were slightly lower at 72-h PA compared to $rScO_2$ values shortly after birth. This suggests downregulation of compensatory mechanisms instead of a relative lack of hemodynamic development in SGA infants as an explanation for values converging toward AGA values. The limited number of severe SGA cases (i.e., BW z-score <–2, n = 18) prevented statistical significance of the effect that being severely SGA has on $rScO_2$ and cFTOE.

We preferred to present "overall" reference curves over presenting numerous curves according to different morbidities. Therefore, the reference curves are valid for a population of preterm infants admitted to the NICU, with inherent morbidity. The generalized additive models for location, scale, and shape (GAMLSS) results were similar to the mixed-model approach. We chose to report the mixed-model procedure because results are easier to interpret and there is more extensive expertise in mixed-model procedures in our institution.

As mentioned before, substantial differences exist between different NIRS sensors.[14,15] The correlation between values obtained with the adult and neonatal sensor is not perfect (R^2 = 0.65), which is probably caused by the *in vivo* nature of our experiment. However, the relation is clearly linear, which has also been demonstrated *in vitro*.[29] Although the difference between the neonatal and adult sensor can be as high as 15% (mean: 10%), trend monitoring is still possible in a way similar to adult sensors. Moreover, the ±2 SD limits provide a "bandwidth" of ~30% which makes the maximum 15% difference less stressing. However, awareness of a possible offset between sensors is crucial when comparing data between patients, institutions, or devices. For example, a $rScO_2$ of 55% seems low but acceptable when using an adult sensor (Figure 2) but is below the –2 SD threshold in all GA groups when using a neonatal sensor (Figure 5). A $rScO_2$ of 55% with the neonatal sensor converts to an adult sensor value of ~40%, which is close to

or below the thresholds (33–50%) reported to be associated with neuronal damage and adverse neurodevelopmental outcome.[5,22,23] Two of these thresholds were established in piglet studies by using devices that are not commercially available.[22,23] Therefore, these thresholds should be used with caution, especially in preterm neonates. Also, higher values pose pitfalls, as most devices have an upper detection limit of 95%. Any value >85% obtained by an adult sensor would register as 95% (i.e., 85 + 10%) with a neonatal sensor, losing the ability to monitor the $rScO_2$ trend. This is particularly relevant for the prognostic value of the $rScO_2$, for example, in asphyxiated neonates.[30,31]

A possible limitation of this study is the generalizability of the results as participants were admitted to a single level III NICU. However, neonatal intensive care in the Netherlands takes place in 10 NICUs and admissions are purely based on geography. Equipment availability was the only factor to prohibit data collection. As unavailability was supposedly random, this influence should be minimal. Moreover, the number of recording setups substantially increased over the years, now ensuring round-the-clock availability. The second limitation is the restriction to the first 72 h of life. This choice was made to encompass the most vulnerable period of life and to limit strain on nursing staff at the same time. The final limitation is clinical practice in our unit regarding the used SaO_2 thresholds (i.e., 85–92%), which might differ from other institutions. The $rScO_2$ results were not corrected for SaO_2 to avoid overly complicating results and because model coefficients (Table 2) changed less than 5% when correcting to a SaO_2 of 90%. Moreover, the cFTOE curves already provide a form of SaO_2 correction. Altogether, we feel confident that the current results are generalizable to other populations of preterm neonates with a GA <32 wk during the first 72 h of life.

Currently, the core application of NIRS on the NICU lies in trend monitoring. For the inexperienced user, we suggest plotting an infants' $rScO_2$ in the appropriate GA-specific reference curve. In case of sudden changes in $rScO_2$ ≥7% (i.e., 1 SD), we recommend evaluation of clinical parameters (e.g., ventilator settings, hemoglobin levels, presence of a hsPDA, medication, perform a cranial ultrasound), but only after ensuring that the measurement setup has not changed (e.g., sensor displacement). Likewise, absolute $rScO_2$ values close to or outside the ±2 SD bands, should trigger an evaluation, similar to what has been done during the SafeBoosC trial (Safeguarding the Brains of our smallest Children).[32] For a more detailed discussion on which parameters to evaluate in case of either low or high levels or $rScO_2$, we refer to the treatment guideline published by the "SafeBoosC" research group.[33]

Conclusion

This study provides reference values for $rScO_2$ and cFTOE measured by NIRS during the first 72 h of life in premature infants. Both $rScO_2$ and cFTOE are influenced by GA, PA, hsPDA, gender, and being born SGA. Furthermore, an equation is provided to extend the results to $rScO_2$ values obtained with a neonatal NIRS sensor. These data provide an additional way for applying NIRS on the NICU, on top of trend monitoring. Furthermore, reliable reference data can be useful in future studies. Indices of cerebral oxygenation have only been suggested to be related to outcome.[5,22] Future research should focus on developing robust indices of cerebral oxygenation that are related to (long-term) outcome and can be used to guide interventions. Our results suggest that GA- and PA-specific thresholds are worth exploring in this regard. The SafeBoosC research group already reported that NIRS can be used to stabilize the cerebral oxygenation in preterm infants.[32]

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PART 2

PATENT DUCTUS ARTERIOSUS

Cerebral oxygenation and echocardiographic parameters in preterm neonates with a patent ductus arteriosus: an observational study

Laura M. L. Dix[1], Mirella M. C. Molenschot[2]
Johannes M. P. J. Breur[2], Willem B. de Vries[1]
Daniel C. Vijlbrief[1], Floris Groenendaal[1]
Frank van Bel[1], Petra M. A. Lemmers[1]

Departments of [1] Neonatology and [2] Pediatric Cardiology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

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CHAPTER 5

Cerebral oxygenation and echocardiographic parameters in preterm neonates with a patent ductus arteriosus: an observational study

Abstract

Background A haemodynamically significant patent ductus arteriosus (hsPDA) is clinically suspected and confirmed by echocardiographic examination. A hsPDA decreases cerebral blood flow and oxygen saturation by the ductal steal phenomenon.

Aim To determine the relationship between echocardiographic parameters, cerebral oxygenation and a hsPDA in preterm infants.

Methods 380 preterm infants (<32 weeks gestational age) born between 2008 and 2010 were included. Blinded echocardiographic examination was performed on the second, fourth and sixth day after birth. Examinations were deblinded when hsPDA was clinically suspected. Regional cerebral oxygen saturation ($rScO_2$) was continuously monitored by near-infrared spectroscopy during 72 h after birth, and afterwards for at least 1 h before echocardiography. Echocardiographic parameters included ductal diameter, end-diastolic flow in the left pulmonary artery, left atrium/aorta ratio and ductal flow pattern.

Results $rScO_2$ was significantly related only to ductal diameter over time. Mixed modelling analysed the course of $rScO_2$ over time, where infants were divided into four groups: a closed duct, an open haemodynamically insignificant duct (non-sPDA), a hsPDA, which was successfully closed during study period (SC hsPDA) or a hsPDA, which was unsuccessfully closed during study period (UC hsPDA). SC hsPDA infants showed the highest $rScO_2$ on day 6, while UC hsPDA infants had the lowest $rScO_2$ values.

Conclusion Ductal diameter is the only echocardiographic parameter significantly related to cerebral oxygenation over time. Cerebral oxygenation takes a different course over time depending on the status of the duct. Low cerebral oxygenation may be suggestive of a hsPDA.

Introduction

Currently, clinical suspicion of a haemodynamically significant patent ductus arteriosus (hsPDA) arises when symptoms occur such as respiratory instability or cardiac murmurs. The diagnosis is subsequently confirmed by echocardiographic examination.[1,2] Echocardiographic parameters that point to a hsPDA include a larger ductal diameter, higher end-diastolic flow in the left pulmonary artery (LPAed), an increased left atrium/aorta ratio (LA/Ao ratio) as well as the ductal flow pattern of the growing or pulsatile type.[3,4] These flow patterns show a left to right shunt through the duct on Doppler examination, where the pulsatile type has a higher peak flow velocity of approximately 1.5 m/s compared with the growing type.[3]

The brain of preterm infants is vulnerable to disturbances in perfusion and oxygenation. The immature brain develops very fast in the third trimester of pregnancy and uses a significant amount of oxygen.[5,6] Also, cerebral autoregulation is limited in preterm infants.[7] Preterm infants with a hsPDA are especially susceptible to brain damage for several reasons. First of all, the redistribution of blood volume through the open duct from the systemic circulation into the pulmonary circulation (the ducal steal phenomenon) results in decreased cerebral perfusion.[8,9] Previous studies reported a decrease in cerebral blood flow (CBF) and oxygenation in presence of a hsPDA, as shown by Doppler examination and near-infrared spectroscopy (NIRS).[8,10] However, not all studies show a statistically significant effect of a duct on cerebral oxygenation.[11,12] Second, a hsPDA has been associated with decreased blood pressure, even despite a compensatory increase in left ventricular output.[13] Finally, a hsPDA has been related to periventricular or intraventricular haemorrhages (PIVH).[14,15] Cerebral perfusion may be affected to various degrees by a hsPDA, depending on the magnitude of ductal steal, autoregulatory ability of the cerebral vasculature and haemodynamic factors such as cerebral perfusion pressure, myocardial function and left ventricular output. The aim of this study was to investigate the association between the ductus arteriosus, echocardiographic parameters and cerebral oxygenation.

Methods

Patients

In this prospective observational study, all infants born <32 weeks of gestational age (GA) admitted to the Neonatal Intensive Care Unit of the Wilhelmina Children's Hospital Utrecht between 2008 and 2010 were included. hsPDA treatment was initiated if clinical suspicion arose with symptoms such as ventilator problems, cardiac murmur or feeding intolerance, and echocardiographic confirmation of the diagnosis. The study was approved by the medical ethical committee of the University Medical Center Utrecht.

Obstetric, intrapartum and neonatal data were obtained from hospital records. Physiological parameters that were monitored included: systemic oxygen saturation (SaO_2) using a pulse-oximetry probe (Covidien, Mansfield, Massachusetts, USA), arterial blood pressure by means of an indwelling catheter and heart rate using gel electrodes. Haemoglobin was determined on a regular base. Cranial ultrasound was performed daily and PIVH was graded according to the classification of Papile et al.[16] Need for blood pressure support was divided into three categories: none: no support or only fluid administration; mild: dopamine ≤5 µg/kg or severe: dopamine >5 µg/kg or the addition of dobutamine, adrenaline or corticosteroids. The use of inotropes was restricted to blood pressure support management. The diagnosis of moderate-to-severe infant respiratory distress syndrome was based on clinical signs and the need for surfactant therapy. Bronchopulmonary dysplasia was diagnosed, if there was a need for additional oxygen at the corrected age of 36 weeks GA. All treatment decisions were made by attending neonatologists. Infants with haemodynamically significant congenital heart defects or chromosomal abnormalities were excluded.

Infants were divided into four different groups according to the status of their duct during the study period. They either had a closed duct, an open but haemodynamically non-significant PDA (non-sPDA, ie, did not receive treatment during the entire study period) or a haemodynamically significant PDA (hsPDA, ie, received treatment during study period). Infants with a hsPDA were subdivided with regard to their response to treatment: either the duct was successfully closed during the study period (SC hsPDA) or the duct was unsuccessfully closed at the end of the study period (UC hsPDA).

Echocardiographic assessment of the ductus arteriosus

Echocardiographic examinations were performed by attending paediatric cardiologists according to study protocol. All cardiologists were well trained and practiced in neonatal echocardiography. Three serial echocardiographic examinations were performed, on the second, fourth and sixth day after birth. Echocardiographic parameters to assess the duct included internal ductal diameter, LPAed, LA/Ao ratio and presence of a ductal flow type associated with a hsPDA, that is, growing or pulsatile flow pattern.[4] Internal ductal diameter was measured on the most constricted point (anatomical diameter based on two-dimensional (2D) echocardiographic examination). The most constricted point was located either by delineating the duct or by visualisation of ductal flow acceleration. In a duct

without visible constriction but with a hsPDA-associated flow pattern, the diameter was measured at the pulmonary end of the duct. hsPDA confirmation on echocardiographic examination was based on ductal diameter >1.4 mm, presence of growing or pulsatile ductal flow pattern and/or LPAed >0.2 m/s and/or a LA/Ao ratio >1.4.[4,17]

Echocardiographic examinations were blinded for neonatologists. Indication to deblind the results of the examinations included respiratory discomfort (supplementary oxygen need, unable to wean from respiratory support) or haemodynamic complications (ie, blood pressure instability, cardiac murmur or wide pulse pressure).

Monitoring of cerebral oxygenation

NIRS-monitored regional cerebral oxygen saturation ($rScO_2$) was used as a reliable parameter of cerebral oxygenation as well as a surrogate of CBF.[18] It is common practice in our neonatal intensive care for all preterm infants with GA <32 weeks to monitor $rScO_2$ during at least 72 h after birth. We used the INVOS 4100/5100C near-infrared spectrometer (Covidien) with a transducer (SomaSensor SAFB-SM, Covidien) containing a light-emitting diode with two near-infrared wavelengths (ie, 730 and 810 nm) and two distant sensors. The INVOS oximeter is a continuous wave spatially resolved spectrometer.[19] It is important to realise when using NIRS to assess cerebral oxygenation that $rScO_2$ can be merely used as a trend monitoring parameter and not as a quantitative measurement. Spatially resolved spectroscopy calculates $rScO_2$ from differences in absorption of near-infrared light.[20,21] The NIRS (small) adult sensor was attached to the frontoparietal side of the infants' head.[22] A stable and reliable 1 h period was selected prior to each echocardiographic examination. A 1 h baseline period was selected between 6 and 12 h after birth. Fractional tissue oxygen extraction (FTOE) was calculated as $(SaO_2 - rScO_2)/SaO_2$. Analysis of $rScO_2$ was performed using Signal Base software (University Medical Center Utrecht, the Netherlands), designed for $rScO_2$ signal analysis. Measurements were considered as non-representative when $rScO_2$ was below 30% or when abundant artefacts were present and arterial oxygen saturation was below 85%.

Statistical analysis

Data are summarised as mean±SD, count and percentage or as median and range, where appropriate. Student's t test, analysis of variance with Tukey honest significant difference correction, Mann–Whitney U test, Pearson's X^2 test or Kruskal–Wallis test was used to compare patient characteristics and differences in dependent variables between the groups. Two main associations were assessed over time. First is the association between

echocardiographic parameters and cerebral oxygenation on the three consecutive time points: 1) second day of life, when the first echocardiographic examination was performed, 2) fourth day of life, during the second echocardiographic examination and 3) sixth day of life, during the third echocardiographic examination. The second association is between the status of the duct and cerebral oxygenation, over the same three time points, with an additional baseline moment: (0) baseline, between 6 and 12 h after birth. In both analyses, the factors GA and being born small for gestational age (SGA) were taken into account as they both can influence cerebral oxygenation. Cerebral oxygenation increases with increasing GA, and being SGA can lead to relative cerebral luxury perfusion.[23] Mixed model analysis was used for statistical analysis. This approach was chosen because it is appropriate in an unbalanced data structure with missing values. Both main effects and interactions were examined. The final model was selected based on the best –2 log-likelihood. Statistical significance was set at $p<0.05$. All statistical analysis was performed with SPSS (IBM Statistics SPSS V.20) or in R for Windows 64-bit, V.3.1.1 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) with the nonlinear mixed-effects package.

Results

A total of 391 infants were included between 2008 and 2010. Eleven infants were excluded for either chromosomal or genetic abnormalities (n=4), metabolic disorders (n=1), congenital anomalies (n=4) or because we were unable to collect data (n=2). This resulted in a study population of 380 infants. Clinical characteristics are shown in Table 1. During the study period, 76 infants developed a hsPDA and were treated with indomethacin (n=61) or surgical ligation (n=15). All infants with a hsPDA were treated with indomethacin as soon as possible after diagnosis was confirmed. When indomethacin failed to close the duct or a contraindication was present, surgical ligation was performed. Subanalysis showed no substantial differences in clinical characteristics between infants treated with indomethacin and infants with surgical ligation. During the first echocardiographic examination, 180 infants had a closed duct and 124 a non-sPDA.

Infants with an open duct were significantly younger and had lower birth weights than infants with a closed duct. There was no significant difference in number of SGA infants between groups. Infants with a hsPDA were generally sicker, for example, a larger proportion was ventilated, suffered from sepsis or needed more blood pressure support. Also, the incidence of retinopathy of prematurity was higher in infants with a hsPDA. Lower GA increased the risk of hsPDA.

Table 1. Clinical characteristics.

Group n = 380	Closed n = 179	non-sPDA n = 125	SC hsPDA n = 32	UC hsPDA n = 44	p-value
Gender, male (%)	93 (52)	63 (50)	15 (47)	24 (55)	ns
Gestational age (wk), mean±SD	30.0±1.6	29.6±1.6	28.3±1.7*#	27.7±2.1**##	
Birth weight (grams), mean±SD	1388±431	1356±330	1026±254*#	1058±287**##	
SGA (<p10), n (%)	15 (8)	5 (4)	5 (16)	4 (9)	ns
Apgar 1 min, median (range)	7 (0-10)	7 (1-10)	5 (0-9)*#	6 (1-9) **##	
Apgar 5 min, median (range)	9 (2-10)	9 (1-10)	8 (3-10)*#	8 (4-10) **##	
aCCS full course, n (%)	144 (80)	95 (76)	22 (66)	36 (82)	ns
Ventilator support, n (%)					<.001
• Not intubated: none, low flow or CPAP	122 (62)	77 (62)	4 (14)	7 (16)	
• Intubated: SIMV or HFO	57 (32)	48 (38)	28 (88)	37 (84)	
IRDS, with surfactant, n (%)	54 (30)	50 (40)	27 (84)	33 (75)	<.001
PIVH, n (%)					ns
• None	146 (82)	89 (72)	23 (72)	30 (68)	
• 1 (Germinal layer)	15 (8)	17 (14)	3 (9)	5 (11)	
• 2 (<50% ventricle)	13 (7)	14 (11)	2 (6)	5 (11)	
• 3 (>50% ventricle)	4 (2)	3 (2)	4 (13)	4 (9)	
• 4 (Venous infarction)	1 (1)	2 (2)	0	0	
Inotropes n (%)					≤.001
• None	149 (83)	103 (82)	15 (47)	18 (41)	
• Mild	11 (6)	5 (4)	0	9 (20)	
• Severe	19 (11)	17 (14)	17 (53)	17 (39)	
Sepsis, n (%)					
• <48h	5 (3)	1 (1)	0	3 (7)	<.001
• >48h	27 (15)	18 (14)	12 (38)	16 (36)	ns
Necrotising enterocolitis, n (%)	4 (2)	3 (2)	1 (3)	1 (2)	ns
BPD, n (%)	4 (2)	3 (2)	1 (3)	3 (7)	ns
Mortality, n (%)	2 (1)	2 (2)	3 (9)	4 (9)	<.05

aCCS: antenatal corticosteroids; BPD: bronchopulmonary dysplasia; non-sPDA: hemodynamically non-significant patent ductus arteriosus; Inotropes: None: no support or only fluid administration, Mild: Dopamine ≤5 µg/kg, Severe: Dopamine >5µg/kg or the addition of Dobutamine, Adrenaline or Corticosteroids; IRDS: infant respiratory distress syndrome; ns: non-significant; PIVH: peri-intraventricular haemorrhage according to Papille classification[16]; SC hsPDA: successfully closed hemodynamically significant patent ductus arteriosus; SGA: small for gestational age; UC hsPDA: unsuccessfully closed hemodynamically significant patent ductus arteriosus. * Closed vs SC hsPDA; ** Closed vs UC hsPDA; #Non-sPDA vs SC hsPDA; ##non-sPDA vs UC hsPDA. p<.05

A hsPDA was present in 41 of the 88 infants (47%) with GA <28 weeks, 22 of 118 infants (19%) with GA between 28 and 30 weeks and 13 of 174 infants (7%) with GA between 30 and 32 weeks GA developed a hsPDA.

In 188 infants, the echocardiographic examination was deblinded: 75 showed a hsPDA, 60 showed a non-sPDA and 53 showed a closed duct. For 158 infants, deblinding occurred during the study period. Indications were circulatory (n=110), pulmonary (n=27), infection (n=3), neurological (n=12), cardiologist request (n=3) or due to other reasons (eg, suspicion of a congenital malformation, n=5). Thirty infants were deblinded after the study period due to minor cardiac malformations, which needed to be re-evaluated at the outpatient clinic.

Cerebral oxygen saturation and echocardiographic parameters

Figure 1 shows NIRS-monitored $rScO_2$ values and the echocardiographic parameters LA/Ao ratio and ductal diameter in the four groups (closed duct, non-sPDA, SC hsPDA and UC hsPDA) on three time points (day 2, 4 and 6 of life). Ductal diameter can only be measured in infants with an open duct. Echocardiographic parameters differed statistically significant between the four patient groups, as shown in Table 2. For the parameter ductal flow pattern 69% of the data were missing, and for LPAed 67% of the data were missing. Therefore, these parameters were not included in the analysis. Mixed model analysis assessed the association between echocardiographic parameters and $rScO_2$, independent of group membership (ie, status of the duct). The effect of time was taken into account, with a random intercept per patient and a fixed effect for $rScO_2$, time, GA, SGA and the echocardiographic parameter. A statistically significant effect was only obtained for the echocardiographic parameter ductal diameter. The best model was obtained with the association between $rScO_2$ and ductal diameter, GA, being SGA and time. The resulting model was: $rScO_2$=36.29–2.38×time–0.95×ductal diameter+3.10×SGA+1.15×GA (all coefficients p<0.05). The LA/Ao ratio did not show a statistically significant relation with $rScO_2$. The same analysis for FTOE did not show a significant relationship with ductal parameters diameter or LA/Ao ratio. Subanalysis with only hsPDA infants did not improve the association between $rScO_2$ and echocardiographic parameters.

Table 2. Cerebral oxygenation and echocardiographic parameters.

	Closed		Non-sPDA			SC hsPDA			UC hsPDA		
	$rScO_2$	LA/Ao	$rScO_2$	LA/Ao	Diam	$rScO_2$	LA/Ao	Diam	$rScO_2$	LA/Ao	Diam
2	68±9	1.40±0.24	66±9	1.46±0.28	1.31±0.52	65±9	1.68±0.26*#	1.89±0.46#	66±9	1.56±0.30‡	1.70±0.59§
4	66±9	1.34±0.21	65±9	1.35±0.24	0.61±0.79	66±8	1.63±0.33*#	0.75±0.87x	62±11	1.53±0.22‡§	1.61±0.69§
6	63±9	1.33±0.24	61±8	1.33±0.24	0.35±0.59	63±6	1.44±0.29		61±11	1.52±0.28‡§	1.23±0.81§

Diam: ductal diameter in mm; Non-sPDA: hemodynamically non-significant patent ductus arteriosus; $rScO_2$: regional cerebral oxygen saturation in %; SC hsPDA: successfully closed hemodynamically significant patent ductus arteriosus; UC hsPDA: unsuccessfully closed hemodynamically significant patent ductus arteriosus. *Closed vs SC hsPDA; #non-sPDA vs SC hsPDA; xUC hsPDA vs. SC hsPDA; ‡Closed vs UC hsPDA; §non-sPDA vs UC hsPDA; p<0.05.

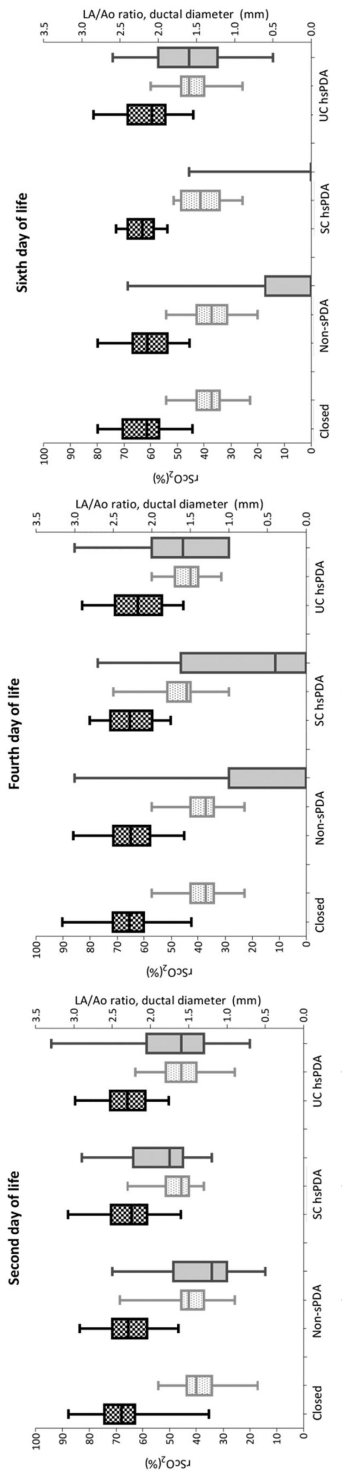

Figure 1: Boxplots of cerebral oxygenation and echocardiographic parameters on the second, fourth and sixth day of life. Infants either have a closed duct, a hemodynamically non-significant Patent Ductus Arteriosus (non-sPDA), a successfully closed hemodynamically significant Patent Ductus Arteriosus (SC hsPDA) or an unsuccessfully closed hemodynamically significant Patent Ductus Arteriosus (UC hsPDA). $rScO_2$: regional cerebral oxygen saturation. LA/Ao: Left Atrium/Aorta ratio. Ductal diameter (mm).

5

Cerebral oxygen saturation and the ductus arteriosus

Over time, mean $rScO_2$ values tended to be lower in infants with an open duct. However, these differences were not statistically significant. Mixed model analysis assessed the course of $rScO_2$ during the first 6 days after birth depending on the status of the duct, with a random intercept per patient and a fixed effect for: time (as categorical factor), GA, SGA, group (by ductal status) and the interaction time×group. Infants were divided into four groups according to the status of their duct during the study period. They either had a closed duct (n=179), an open non-sPDA (n=125), a hsPDA (n=76), which was either effectively treated (SC hsPDA, n=32) or remained open at the end of the study period (UC hsPDA, n=44). The different slopes and corresponding p values are shown in Table 3. Mean $rScO_2$ is significantly determined by time, GA, group (ductal status) and the interaction between time×group. Mean blood pressure had no significant effect.

Figure 2 shows an example of the course of cerebral oxygen saturation over time in infants of 29 weeks GA. Based on the model shown in Figure 2, infants who developed a hsPDA started with the lowest $rScO_2$. After 6 days, infants with a SC hsPDA showed the highest $rScO_2$, infants with a closed duct had slightly lower $rScO_2$ values followed by infants with a non-sPDA and infants with a UC hsPDA showed the lowest $rScO_2$. The inverse association existed for FTOE. Infants with a SC hsPDA showed the highest $rScO_2$ with the lowest FTOE, while infants with an UC hsPDA showed the lowest $rScO_2$ with the highest FTOE after 6 days. Subanalysis with hsPDA infants showed that $rScO_2$ was lower in infants who underwent surgery than infants treated with indomethacin (mean 55.3%±9.0 vs mean 63.4%±8.4 SD; p<0.05).

Discussion

This present study shows that cerebral oxygenation is significantly related only to the echocardiographic parameter ductal diameter, together with GA and being SGA over time. Although not significant, a trend of lower cerebral oxygenation and higher LA/Ao ratio is seen in infants with a hsPDA. Depending on the status of the duct, cerebral oxygenation takes a different course over time. Consistent with previous findings, infants who were surgically ligated showed lower cerebral oxygen saturation than infants who received pharmacological treatment.[24] These findings support our hypothesis that a hsPDA has a systemic effect through the ductal steal phenomenon, leading to a reduction of cerebral perfusion and oxygenation. However, a venous component cannot be excluded. An increased venous compartment due to venous congestion or vasodilatation in the brain could decrease cerebral oxygen saturation.

Table 3. Mixed-effects model of cerebral oxygenation

	Coefficient	SD	p-value
Constant	33.46	6.67	<.001
Time (categorical)			
• 1	0.42	0.98	ns (.667)
• 2	-1.9	1.03	ns (.059)
• 3	-5.1	1.36	<.001
GA	1.15	0.22	<.001
Group: (ref: Closed)			
• Non-sPDA	-0.21	1.36	ns (.876)
• SC hsPDA	-4.55	1.92	.018
• UC hsPDA	-3.65	1.84	.048
Interactions: Time*Group (ref: Closed)			
• Time1 * Non-sPDA	-2.16	1.51	ns (.154)
• Time2 * Non-sPDA	-0.45	1.58	ns (.778)
• Time3 * Non-sPDA	-1.40	2.04	ns (.492)
• Time1 * SC hsPDA	2.72	2.18	ns (.213)
• Time2 * SC hsPDA	6.60	2.20	.003
• Time3 * SC hsPDA	7.03	2.60	.007
• Time1 * UC hsPDA	4.17	2.00	.036
• Time2 * UC hsPDA	2.64	2.07	ns (.203)
• Time3 * UC hsPDA	4.71	2.40	.049

GA: gestational age; Non-sPDA: hemodynamically non-significant patent ductus arteriosus; SC hsPDA: successfully closed hemodynamically significant patent ductus arteriosus; UC hsPDA: unsuccessfully closed hemodynamically significant patent ductus arteriosus

A hsPDA has been associated with low cerebral oxygen saturation,[8] and PIVH.[3,15,25] The use of cerebral oxygenation as a screening tool to detect a hsPDA has been suggested previously.[12] Although it should be noted that NIRS determined $rScO_2$ can be merely used as a trend monitoring parameter to assess changes in cerebral oxygenation and not as a quantitative measurement. It estimates changes in oxygenation with an assumption of path length of the near-infrared light bundle.[26,27] Assessment of cerebral oxygenation over time can alert the clinician to a (developing) hsPDA. As there is still a lot of debate concerning hsPDA diagnosis and treatment and solid criteria are lacking, cerebral oxygenation could be of additional value in the decision-making process.

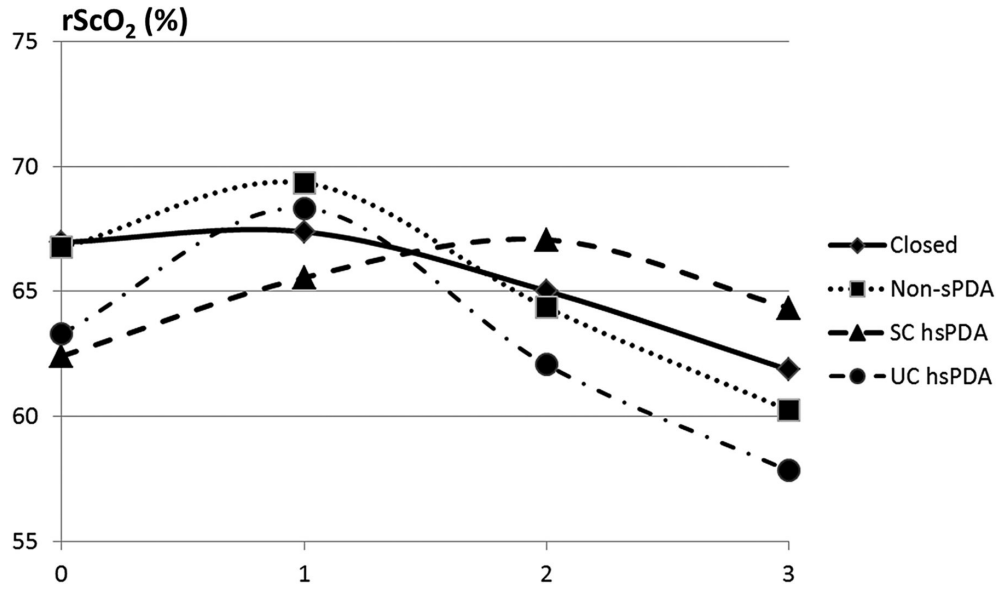

Figure 2. Regional cerebral oxygen saturation ($rScO_2$) for infants of 29 weeks gestational age during the first 6 days of life depending on the status of the duct: closed, haemodynamically non-significant patent ductus arteriosus (non-sPDA), successfully closed haemodynamically significant patent ductus arteriosus (SC hsPDA closed) or unsuccessfully closed hsPDA (UC hsPDA). Time points: (0) baseline within 12 h after birth; (1) day 2; (2) day 4; (3) day 6.

It is important to realize while interpreting these results that the haemodynamic impact of ductal steal may be quite variable.[3] Ductal flow depends on changes in pulmonary pressure and systemic vascular pressure, both of which are very dynamic and may cause temporary changes in the magnitude and even direction of ductal shunting.[3] The consequences of a hsPDA may differ between infants, and hsPDA scoring systems have already been suggested.[28–30] To date, there is no real gold standard for the diagnosis of a hsPDA, and more precisely the magnitude of ductal flow and steal. After echocardiographic examination, the attending neonatologist draws the final conclusion. It may be unclear what the exact differences between a hsPDA and a non-sPDA are, as diagnosis is partly subjective. The fluctuating magnitude of the shunt and ductal steal over time prohibits an objective distinction. Also, echocardiographic parameters may be difficult to interpret early in the course of a (developing) hsPDA. Ductal diameter is measured by 2D echocardiography on the most constricted point, which may be difficult to identify. The LA/Ao ratio is derived of left atrium enlargement after volume overload. It signifies increased workload of the left heart after extensive ductal shunting, it does not directly assess haemodynamic severity of the duct.[31] It takes time for left atrium enlargement to

develop and our centre starts treatment early, so it might not be sufficiently developed yet during the study period. LPAed and ductal flow pattern both seemed promising as reflections of hsPDA severity, as they are directly related to ductal steal.[32] Unfortunately, our study contained too many missing values to make valid statements concerning the course of these parameters over time. However, a previous study has shown that ductal diameter is significantly associated with ductal flow pattern.[33] Although intra-rater and inter-rater variability of echocardiographic examinations were not included in the study design, all examinations were performed by well-trained and experienced paediatric cardiologists. Echocardiographic examination in itself can challenge the clinical stability of sick preterm infants, sometimes requiring adaptation of ventilator settings. Therefore, non-invasive monitoring with NIRS may sometimes be a reasonable alternative to assess hsPDA severity by evaluating the effect of ductal steal on cerebral oxygenation. Without a gold standard for hsPDA diagnosis, assessment of cerebral saturation can aid the clinician together with echocardiographic examination. Our group previously showed that cerebral oxygenation is lower in infants with a hsPDA. Prolonged low cerebral oxygenation ($rScO_2$ <40%) has been associated with brain damage.[34,35] $rScO_2$ recovers to normal values after ductal closure.[8]

A hsPDA is a common complication in all preterm infants, but occurs most often in the youngest infants. In this study, the prevalence of hsPDA was also highest in infants born before 28 weeks of GA. However, in our centre all infants born before 32 weeks of gestation with a hsPDA are usually treated early and proactively. There is an ongoing debate among neonatologist when and for which patients treatment is most suitable. To increase generalizability of our results to centres who only treat infants with GA <28 weeks, we have added GA as an independent factor in our analyses.

$rScO_2$ takes a different course over time depending on the status of the duct. Overall, a general decline is seen over time. This finding is in accordance with a previous study by our group, providing reference values of cerebral oxygenation during the first 3 days of life.[23] This decline is presumably caused by physiological changes in haemoglobin, as well as relative low haemoglobin levels due to frequent blood testing on a neonatal intensive care unit. Roche-Labarbe et al[36] reported a similar declining pattern. As stated previously, in our centre hsPDA treatment is initiated early. This is presumably why extremely low values of cerebral oxygenation were not observed during the first 6 days after birth. The reasoning behind early treatment is underlined by a recent study by Rozé et al, who reported that early screening and treatment for a hsPDA was associated with lower in-hospital mortality and likelihood of pulmonary haemorrhage.[37] In our study, infants with a non-sPDA show slightly lower cerebral oxygenation after 6 days and a sharper decline over time compared with infants with a closed duct. This could mean a (small) haemodynamic effect of the duct after all, and the term haemodynamically insignificant might not be entirely appropriate. Cerebral oxygenation is influenced by perfusion as well as oxygen transport capacity. Haemoglobin and SaO_2 were kept within normal range. The influence of other factors affecting tissue oxygenation other than hsPDA, such as circulatory complications, was negligible in our study population. Future research should focus on the contributing effect of NIRS-monitored cerebral oxygenation in hsPDA diagnosis, especially when echocardiographic examination is inconclusive or in contradiction with clinical symptoms.

Conclusion

Cerebral oxygenation is related to ductal diameter during the first 6 days of life in infants born <32 weeks GA, together with GA and being SGA. A larger diameter is associated with a lower cerebral oxygen saturation. There appears to be a trend, although not significant, towards lower cerebral oxygenation and a higher LA/Ao ratio. Cerebral oxygenation takes a different course over time, depending on the status of the duct. Infants with an effectively closed hsPDA recover to normal cerebral oxygenation, whereas infants with a hsPDA that remains open show the lowest values of cerebral oxygenation at day 6. These infants could represent a separate patient group who do not respond well to treatment, or are recognised or develop a hsPDA at an older stage. Infants with an open but haemodynamically insignificant ductus arteriosus show lower cerebral oxygenation and a sharper decline over time compared with infants with a closed duct. This could be due to the ductal steal phenomenon. Monitoring cerebral oxygenation can help the clinician in diagnosing and evaluating treatment of a hsPDA.

5

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Reduction in cerebral oxygenation due to patent ductus arteriosus is pronounced in small-for-gestational-age neonates

6

Emily Cohen[1,2], Laura M. L. Dix[1]
Willem Baerts[1], Thomas Alderliesten[1]
Petra M. A. Lemmers[1], Frank van Bel[1]

[1] Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands.
[2] The Ritchie Centre, Hudson Institute of Medical Research and Department of Paediatrics, Monash University, Melbourne, Vic., Australia

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CHAPTER 6

Reduction in cerebral oxygenation due to patent ductus arteriosus is pronounced in small-for-gestational-age neonates

Abstract

Background A haemodynamically significant patent ductus arteriosus (hsPDA) reduces cerebral oxygenation in appropriate-for-gestational-age (AGA) preterm neonates. Reduced cerebral oxygenation has been associated with brain injury. Preterm small-for-gestational-age (SGA) neonates show higher cerebral oxygenation than AGA peers throughout the first postnatal days. To date, no studies have investigated the effect of hsPDA on cerebral oxygenation in preterm SGA neonates.

Objective We aimed to assess the effect of hsPDA on cerebral oxygenation in preterm SGA neonates compared to AGA peers. We hypothesised that higher baseline cerebral oxygenation would reduce the impact of hsPDA on cerebral oxygenation in preterm SGA neonates.

Methods We monitored regional cerebral oxygen saturation ($rScO_2$) with near-infrared spectroscopy and calculated the cerebral fractional tissue oxygen extraction (cFTOE) for 72 h after birth. Retrospective analysis compared 36 preterm SGA neonates (birth weight <10th percentile, 18 with hsPDA) to 36 preterm AGA neonates (birth weight 20th to 80th percentile, 18 with hsPDA).

Results In contrast to the other groups, SGA-hsPDA neonates demonstrated a significant fall in $rScO_2$ [69% (SEM 2.5) at 4-8 h to 61% (2.7) at 68-72 h, $p < 0.001$] with a concurrent rise in cFTOE [0.26 (0.026) at 4-8 h to 0.34 (0.030) at 68-72 h, $p < 0.001$].

Conclusion Contrary to our hypothesis, hsPDA had a significant negative effect on cerebral oxygenation in preterm SGA neonates. Future studies should explore the potential benefits of early screening and treatment for hsPDA on long-term neurodevelopmental outcome in preterm SGA neonates.

Introduction

A haemodynamically significant patent ductus arteriosus (hsPDA) reduces cerebral oxygenation in appropriate-for-gestational-age (AGA) preterm neonates.[1] This reduction is thought to be the result of diminished cerebral perfusion caused by left-to-right ductal shunting as well as lower blood pressure that occur in the presence of an hsPDA.[1] Reduced cerebral oxygenation has been related to brain injury and a compromised neurodevelopmental outcome,[2,3] suggesting that a timely diagnosis and treatment of hsPDA to prevent or redress a fall in cerebral oxygenation may be beneficial.[4]

The effect of hsPDA on cerebral oxygenation in small-for-gestational-age (SGA) preterm neonates has not yet been explored. This matter is particularly interesting, as our group has previously shown that SGA preterm neonates demonstrate brain sparing-induced elevation of cerebral oxygenation throughout the first days of life.[5] A higher cerebral oxygenation baseline may allow SGA neonates to maintain their cerebral oxygenation at control levels despite the presence of hsPDA.[6] In this study we aimed to assess the effects of hsPDA on cerebral oxygenation in SGA compared to AGA preterm neonates.

Methods

Patients

This case-control study constitutes a retrospective subanalysis of a prospective cohort study on reference values of cerebral oxygenation in preterm neonates admitted to the neonatal intensive care unit of the Wilhelmina Children's Hospital in the Netherlands between 2005 and 2013.[7] The patient selection process is demonstrated in Figure 1. All SGA neonates (as defined by a birth weight below the 10th percentile for gestational age on the Fenton growth curve[8] who developed an hsPDA within the first week of life were identified from this cohort. All neonates with clinical suspicion of hsPDA underwent echocardiography performed by our paediatric cardiologist. hsPDA was subsequently defined as a PDA confirmed to be haemodynamically significant on echocardiography (left atrial to aortic root ratio >1.4 and/or internal ductal diameter >1.4 mm and/or left pulmonary artery end-diastolic flow >0.2 m/s and/or presence of growing or pulsatile ductal flow pattern[9,10] and treated with indomethacin or surgically ligated.[11] The exclusion criteria were chromosomal abnormalities, congenital abnormalities influencing the systemic and/or cerebral circulation (including congenital heart disease other than hsPDA), proven perinatal infection, perinatal asphyxia,[12] and grade IV intraventricular haemorrhage.[13] Eighteen SGA-hsPDA neonates (13 males) were eligible for further analysis. We

were unable to find gestational age-matched controls for each SGA-hsPDA subject in our database. Therefore, using the Microsoft Excel RAND function, we randomly selected SGA neonates without hsPDA and AGA neonates with/without hsPDA (birth weight 20th to 80th percentile) to serve as control subjects. We have previously shown that gender significantly influences cerebral oxygenation.[5,7] To avoid bias caused by different gender distributions within the groups, the selection of control subjects was performed within the same male-to-female ratio as present in our SGA-hsPDA group.

Data collection

Obstetric, intrapartum, and neonatal data were retrieved from the maternal and neonatal records. Foetal Doppler measurements were collected when available. A middle cerebral artery pulsatility index below the 5th percentile was considered abnormal and a sign of prenatal brain sparing.[14] Neonatal data included a daily blood pressure support score adapted from Krediet et al.[15] and a respiratory support classification, categorized as assisted ventilation (synchronized intermittent mandatory ventilation or high-frequency oscillatory ventilation) or spontaneous breathing (no support, low flow or continuous/bilevel positive airway pressure). In hsPDA neonates, the time of hsPDA diagnosis and hsPDA closure were expressed as postnatal age at the time of the cardiac ultrasound that confirmed the presence and absence, respectively, of hsPDA.

To investigate cerebral oxygenation, regional cerebral oxygen saturation ($rScO_2$) and cerebral fractional tissue oxygen extraction (cFTOE) were monitored using near-infrared spectroscopy throughout the first 72 h of life (INVOS 5100C with small adult sensor SomaSensor SAFB-SM; Covidien/Medtronic, Boulder, Colo., USA). These data were collected together with standard physiological data including oxygen saturation by pulse oximetry (SpO_2) and mean arterial blood pressure (MABP) by an indwelling arterial catheter. This study was approved by the Medical Ethical Committee of the University Medical Centre Utrecht.

Data analysis

Data were analysed with software developed in-house (SignalBase®, University Medical Centre Utrecht, The Netherlands). Artefacts due to movement, handling and technical errors were removed manually. Data were averaged for 1-hour periods reflecting the neonate's postnatal age in hours.[7] Mean 1-hour values calculated from less than 10 min of reliable data were excluded from the analysis.[7] For the current study, these data were subsequently averaged over blocks of 4 h. Data beyond hsPDA closure, as confirmed on echocardiography, were excluded from the analysis.

Data were statistically analysed using IBM SPSS for Windows V22. Clinical data were analysed using the X^2 or Kruskal-Wallis test with a step-wise step-down procedure. Outliers within physiological and cerebral oxygenation data were truncated. These data were analysed using a mixed model approach taking into account the individual participant as a random effect nested within the group. Gender and gestational age were included in the model as covariates.[5,7] For cerebral oxygenation data, however, gestational age did not show a significant effect and worsened the model fit, and was thus omitted from these analyses.

Clinical data are represented as n (%) or the median and range, and physiological and cerebral oxygenation data as the mean and SEM. The graphs illustrate raw data before truncation.

Results

There was no statistically significant difference in the overall prevalence of hsPDA between SGA and AGA neonates (26/105, 25% vs. 172/656, 26%, p = 0.43). The clinical data are shown in Table 1. Gestational age at birth was significantly different between the four groups (p < 0.001); however, the gestational age of SGA-hsPDA and AGA-hsPDA neonates was comparable. The postnatal age at the time of hsPDA diagnosis (31 and 47 h, p = 0.23) and hsPDA diameter (2.3 and 2.2 mm, p = 0.50) were not different between SGA and AGA neonates. Neonates with hsPDA were more frequently mechanically ventilated (p < 0.001), were more often in need of surfactant therapy (p < 0.001) and received more intensive blood pressure support (p = 0.01). However, these parameters were not different between SGA-hsPDA and AGA-hsPDA neonates.

For the majority of SGA pregnancies (83%) prenatal Doppler measurement of the middle cerebral artery pulsatility index was available and was classified as abnormal in 77% of the cases. SGA pregnancies tended to be more frequently related to pre-eclampsia (p = 0.06), were more often delivered by Caesarean section (p < 0.001) and their placental weight for gestational age was more frequently below the 10th percentile (p < 0.001).

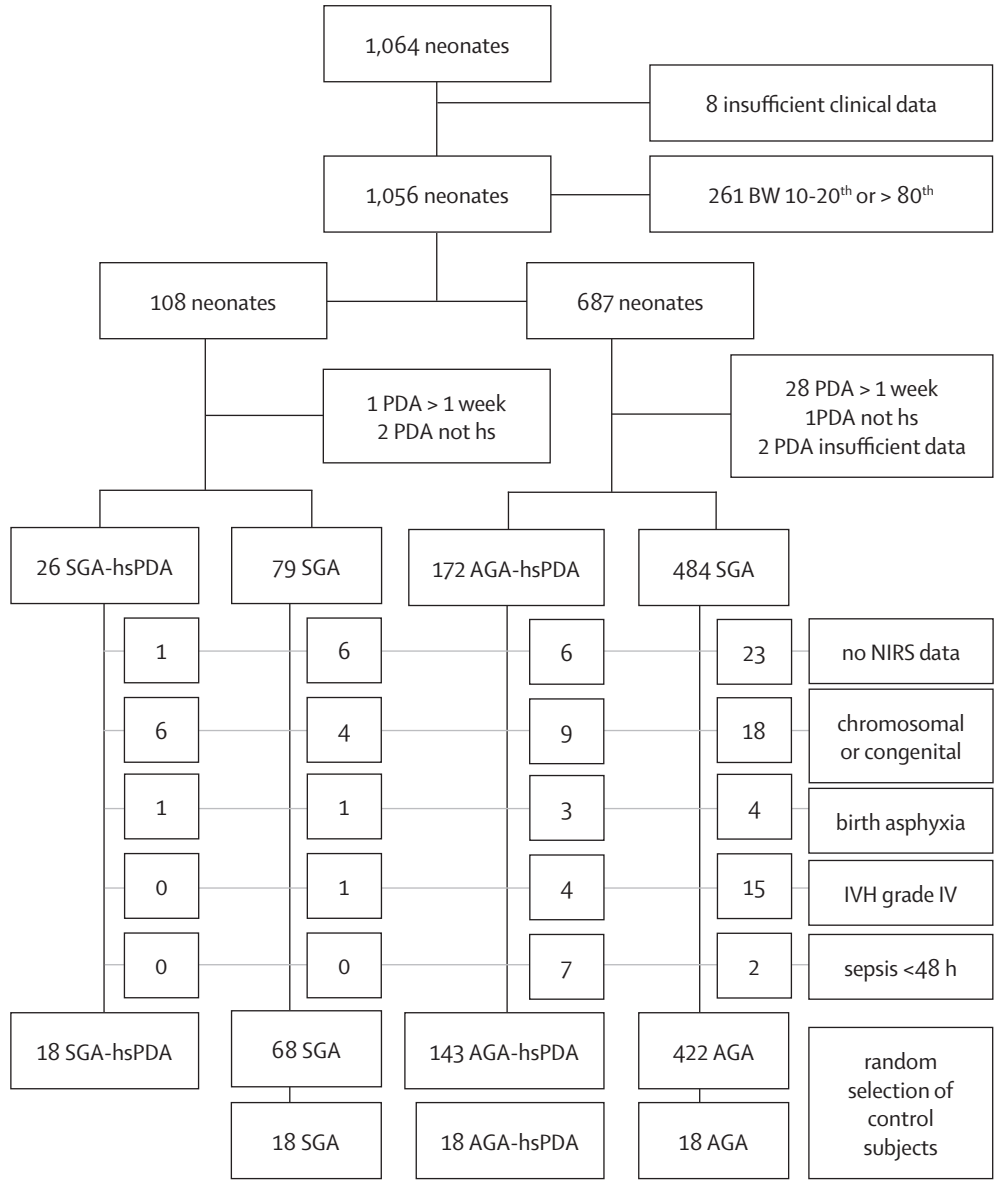

Figure 1. Patient selection. BW = Birth weight; PDA >1 week = developed hsPDA beyond 1 week of life; IVH = intraventricular haemorrhage; NIRS = near-infrared spectroscopy.

Table 1. Clinical characteristics.

	SGA-hsPDA	SGA	AGA-hsPDA	AGA	P
Male	13 (72)	13 (72)	13 (72)	13 (72)	n.a.
GA, weeks	27^{+6} (25^{+3}–30^{+4})	30^{+4} (26^{+4}-32)	27^{+3} (24^{+3}-31^{+1})	28^{+6} (25-31^{+5}	<0.001
Birth weight, g	675 (485-1000)	860 (645-1235)	995 (650-1640)	1213 (810-1770)	<0.001
Postnatal age at hsPDA diagnosis, h	31 (6-122)	n.a.	47 (10-115)	n.a.	0.23
Diagnosed during study period (≤72h)	16 (89)	n.a.	15 (83)	n.a.	0.50
hsPDA diameter, mm	2.3 (1.6-3.4)	n.a.	2.2 (1.5-3.3)	n.a.	0.50
Pre-eclampsia	9 (50)	9 (50)	4 (22)	3 (17)	0.006[a]
Antenatal corticosteroids	15 (83)	17 (78)	13 (72)	12 (67)	0.69
Delivery by caesarean section	16 (89)	18 (100)	8 (44)	8 (44)	<0.001[a]
Apgar 5 min	8 (5-9)	9 (6-10)	8 (5-9)	9 (8-10)	0.002[b]
Umbilical artery pH	7.26 (7.17-7.33)	7.22 (7.03-7.37)	7.30 (7.17-7.31)	7.27 (7.08-7.39)	0.16
First postnatal lactate mmol/l	7 (2.2-15.1)	5.4 (2-10.8)	4.1 (1.9-10)	3.8 (1.4-7.5)	0.009[a]
Predominant form respiratory support					<0.001[b]
• Low flow/CPAP/BIPAP	5 (28)	15 (28)	5 (28)	14 (78)	
• SIMV/HFOV	13 (72)	3 (17)	13 (72)	4 (22)	
Need for surfactant					<0.001[b]
• Yes	16 (89)	5 (28)	15 (83)	6 (33)	
• No	2 (11)	13 (72)	3 (17)	12 (67)	
Predominant form blood pressure support (15)					0.01[b]
• No	9 (50)	14 (78)	10 (56)	16 (89)	
• Mild	2 (11)	2 (11)	4 (22)	2 (11)	
• Moderate-intensive	7 (39)	2 (11)	4 (22)	0 (0)	
IVH during study period	2 (11)	1 (6)	4 (22)	3 (17)	0.671

Values are presented as n (%) or median (range). [a] SGA vs. AGA; [b] hsPDA vs. no hsPDA. GA=gestational age; CPAP=continuous positive airway pressure; BIPAP=bilevel positive airway pressure; SIMV=synchronized intermittent mandatory ventilation; HFOV=high-frequency oscillatory ventilation; IVH=intraventricular haemorrhage; n.a.=not applicable.

Haemodynamics and Cerebral Oxygenation Data: only data beyond 4 h postnatal age were used for analysis due to a large proportion of missing data over the first 4 h of life (69%).

Haemodynamics

Figure 2 shows the changes in MABP, pulse pressure and SpO_2 for the four groups throughout the first 72 h of life. MABP was not significantly different between the four groups (p = 0.84) and increased with advancing postnatal age. This increase was less pronounced in neonates with hsPDA (p < 0.001), although there was no difference between SGA-hsPDA and AGA-hsPDA neonates (p = 0.09).

Compared to SGA and AGA neonates without hsPDA, AGA-hsPDA neonates had a greater pulse pressure [AGA-hsPDA 22 mm Hg (SEM 1.0) vs. SGA 16 mm Hg (1.1) and AGA 16 mm Hg (1.0), respectively, p = 0.001 for both] and lower SpO_2 [AGA-hsPDA 93% (0.6) vs. SGA 96% (0.6), p = 0.002, and AGA 95% (0.5), respectively, p = 0.01]. Pulse pressure [19 mm Hg (0.1)] and SpO_2 [94% (0.5)] did not differ between SGA-hsPDA neonates and the other groups.

Cerebral oxygenation

Figure 3 demonstrates the changes in $rScO_2$ and cFTOE for the four groups throughout the first 3 postnatal days. At a postnatal age of 4-8 h, SGA neonates demonstrated significantly higher $rScO_2$ and lower cFTOE values than AGA neonates [71% (1.7) vs. 62% (1.7), p < 0.001, and 0.25 (0.018) vs. 0.34 (0.018), p = 0.001, respectively]. hsPDA resulted in significantly lower $rScO_2$ [63% (1.9) vs. 70% (1.7), p = 0.003] and higher cFTOE [0.33 (0.020) vs. 0.27 (0.019), p = 0.03] by 68-72 h. An important finding was that changes in $rScO_2$ and cFTOE with advancing postnatal age were significantly different between SGA-hsPDA neonates and the other groups (p < 0.01 for all). In contrast to the other groups, SGA-hsPDA neonates demonstrated a significant fall in $rScO_2$ [69% (2.5) at 4-8 h to 61% (2.7) at 68-72 h, p < 0.001] and a concurrent rise in cFTOE [0.26 (0.026) at 4-8 h to 0.34 (0.030) at 68-72 h, p < 0.001]) throughout the first 3 postnatal days.

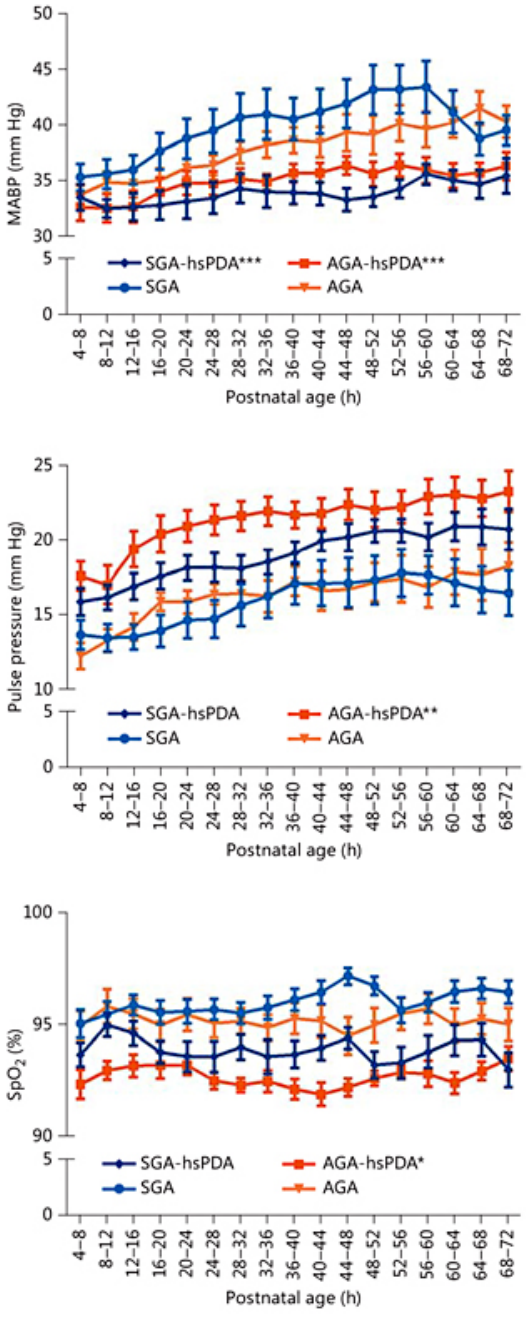

Figure 2: MABP, pulse pressure and SpO_2 changes for the four groups throughout the first 3 postnatal days (mean ± SEM). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. SGA and AGA without hsPDA.

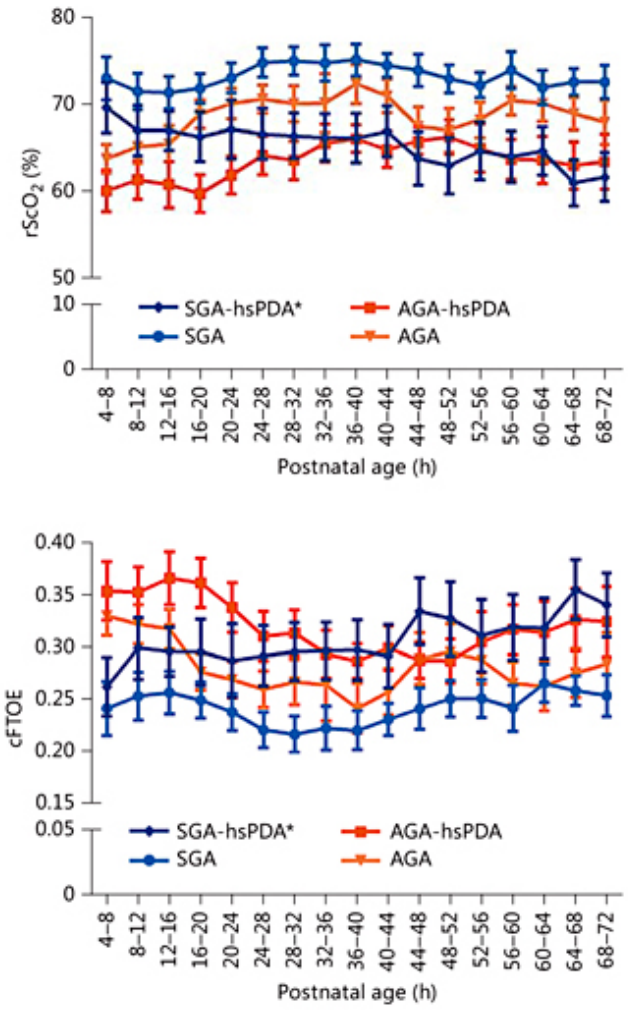

Figure 3: Changes in $rScO_2$ and cFTOE for the four groups throughout the first 3 postnatal days (mean ± SEM). * $p < 0.001$ compared to the other groups.

Discussion

hsPDA lowers cerebral oxygenation. In contrast to our hypothesis, this effect was pronounced in SGA neonates as demonstrated by a significant fall in cerebral oxygenation over the first 72 h. Although neonates can be constitutionally small, it is likely that a large proportion of our preterm SGA neonates suffered from intrauterine growth restriction (IUGR). This hypothesis is supported by the higher rate of pre-eclampsia and instrumental delivery, the smaller placental size and high rate of abnormal middle cerebral artery pulsatility index in SGA pregnancies. The IUGR foetus displays typical haemodynamic alterations, including redistribution of its cardiac output to preserve oxygen and nutrient supply to the brain ('brain sparing').[6] Our group has previously shown that this brain-sparing effect is postnatally sustained up to 72 h.[5,7] Nevertheless, normalisation — or a trend toward normalisation — of cerebral haemodynamic parameters throughout the first few days of life has also been observed, which could indicate that the cerebral circulatory adaptations following IUGR are transitory.[7,16] Physiological downregulation of compensatory mechanisms may in part explain the observed decline in cerebral oxygenation of our SGA-hsPDA neonates.[7]

However, the conventional idea of brain sparing as a protective mechanism has been challenged over recent years.[6] New insights suggest that chronic intrauterine hypoxia results in cerebrovascular remodelling,[17] which may limit the cerebral autoregulatory response to hypoperfusion.[6] In fact, our SGA-hsPDA neonates demonstrated similar MABP, pulse pressure and SpO_2 to AGA-hsPDA neonates. Yet the impact of hsPDA on their cerebral oxygenation appeared more pronounced, as demonstrated by a significant fall in cerebral oxygenation throughout the first 72 h of life, which was not observed in AGA-hsPDA neonates. This pronounced fall in cerebral oxygenation may thus be related to impaired cerebral autoregulation following IUGR.

IUGR is associated with systemic vascular remodelling.[18] Histological changes of the ductus arteriosus have also been reported.[19] These ductal changes may explain why hsPDA has previously been reported to occur more frequently and at an earlier postnatal age in IUGR compared to AGA neonates.[20,21] However, our study did not reveal differences in either the prevalence or time of diagnosis of hsPDA. Rakza et al.[20] reported a larger hsPDA diameter in IUGR neonates compared to AGA peers. Cerebral oxygenation appears to be related to the ductal diameter.[22] In our cohort the hsPDA diameter was similar in SGA and AGA neonates, however, and can thus not explain the differences observed between the groups.

The neonate's condition - including haemodynamic and respiratory status as well as haemodynamic and respiratory support - can influence ductal patency and affect the systemic and cerebral circulation. Neonates diagnosed with proven sepsis during the first postnatal days were therefore excluded from the analysis. Neonates with hsPDA were more often in need of surfactant therapy and were more frequently mechanically ventilated. They also received more intensive blood pressure support than neonates without hsPDA. There was, however, no difference in these parameters between SGA-hsPDA and AGA-hsPDA neonates. Moreover, our SGA-hsPDA neonates demonstrated similar MABP, pulse pressure and SpO_2 values to AGA-hsPDA neonates. Although SGA neonates suffered from the unfavourable intrauterine environment, as demonstrated by the higher first postnatal lactate, we believe that the clinical condition of our SGA-hsPDA and AGA-hsPDA group was similar and cannot explain the observed differences in cerebral oxygenation.

The interpretation of the results of the current study is limited by its retrospective design. Firstly, echocardiography to diagnose hsPDA was performed on clinical suspicion of hsPDA and, thus, the timing of echocardiography was not consistent between neonates. Moreover, neonates without clinical suspicion of hsPDA did not routinely undergo echocardiography. Also, the lack of a standardized study protocol may have created bias.

Secondly, we were unable to select gestational age-matched controls for our SGA-hsPDA subjects, resulting in a statistically significant difference in gestational age between the groups. Although gestational age has previously been shown to influence cerebral oxygenation,[7] we found no association between gestational age and $rScO_2$ or cFTOE within our (small) cohort. Moreover, the gestational age of SGA-hsPDA and AGA-hsPDA neonates was comparable. We thus believe that gestational age alone cannot explain the significantly different time course of $rScO_2$ and cFTOE between SGA- and AGA-hsPDA neonates. Thirdly, cerebral oxygenation measures were not studied beyond 72 h of life and the impact of hsPDA on cerebral oxygenation beyond this point in time cannot be investigated. Also, this study did not investigate the long-term neurodevelopmental outcome of the cohort. Although beyond the scope of this paper, we can thus not conclude whether the observed changes in cerebral oxygenation are of clinical importance. Reduced cerebral oxygenation has been related to a poorer neurodevelopmental outcome.[2] In the current study, SGA-hsPDA neonates showed a significant reduction in cerebral oxygenation. Yet values remained within population limits[7] and our observation may thus not be of clinical significance. Nevertheless, unstable cerebral oxygenation - even within normal limits - has been associated with brain injury.[3,23] Early screening and treatment of hsPDA to redress potentially harmful fluctuations and prevent a further decline in cerebral oxygenation may thus be beneficial to improve outcomes within this population.

It is widely accepted that hsPDA is related to a range of adverse outcomes, although clear evidence to support long-term neurodevelopmental benefits of hsPDA treatment is lacking.[24] The current literature, however, has not taken into account measures of cerebral oxygenation to quantify the haemodynamic impact of hsPDA. Moreover, no distinction has been made between IUGR and AGA infants. IUGR is related to an increased risk of neurodevelopmental compromise.[25] IUGR neonates thus form a subgroup of infants at particular risk of adverse outcomes that may benefit from early screening and therapy for hsPDA to prevent potentially harmful fluctuations in cerebral oxygenation. A recent study by Madeleneau et al.[26] revealed that the risk of ibuprofen treatment failure increases with the degree of growth restriction. When treated early, however, good therapeutic response rates can be achieved in IUGR neonates.[20] These findings insinuate that a timely diagnosis and subsequent treatment of hsPDA in IUGR neonates may be of benefit.

Conclusion

Contrary to our hypothesis, SGA preterm neonates show a pronounced decline in cerebral oxygenation due to a hsPDA. Although the underlying pathophysiological mechanisms and the clinical consequences of this pronounced fall in cerebral oxygenation are yet to be elucidated, early screening and treatment of hsPDA in this population may be warranted to prevent potentially harmful fluctuations in cerebral oxygenation and improve the neurodevelopmental outcome.

Disclosure statement

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Early end-tidal carbon monoxide levels, patency of the ductus arteriosus and regional cerebral oxygenation in preterm infants

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Laura M. L. Dix[1], Cornelie A. Blok[1]
Petra M. A. Lemmers[1], Niek E. van der Aa[1]
Mirella M. C. Molenschot[2], Hendrik J. Vreman[3]
Tannette G. Krediet[1], Frank van Bel[1]

Departments of [1] Neonatology and [2] Pediatric Cardiology, Wilhelmina Children's Hospital,University Medical Center Utrecht, Utrecht, The Netherlands. [3] Neonatal and Developmental Medicine Laboratory, Department of Pediatrics, Stanford University School of Medicine, Stanford, California, USA

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CHAPTER 7

Early end-tidal carbon monoxide levels, patency of the ductus arteriosus and regional cerebral oxygenation in preterm infants

Abstract

Background Carbon monoxide (CO), a relaxant regulator of muscle tone and marker of oxidative stress and inflammation, can be measured in exhaled air by determination of end-tidal CO corrected for CO in ambient air (ETCOc).

Objective Increased endogenous production of CO may influence patency of the ductus arteriosus, cerebral perfusion and, subsequently, cerebral oxygenation. The aim was to study the relation between early ETCOc levels, hemodynamically significant patent ductus arteriosus (hsPDA) and cerebral oxygenation ($rScO_2$) in preterm infants <32 weeks' gestational age and determine predictive values of ETCOc for hsPDA.

Methods ETCOc was measured in 91 infants within the first 24 h after birth. A hsPDA was diagnosed according to echocardiographic indices. In 78/91 infants, $rScO_2$ was monitored with near-infrared spectroscopy to assess cerebral oxygenation.

Results ETCOc values were significantly higher in infants who subsequently developed hsPDA (2.3 ± 0.7 ppm) vs. no-hsPDA (1.7 ± 0.6 ppm), $p < 0.001$. With a cut-off value of 2.5 ppm, positive and negative predictive values of ETCOc for hsPDA were 55 and 88%, respectively. $rScO_2$ values were not different between the two groups (64 ± 1 vs. 65 ± 3%, NS).

Conclusion The higher ETCOc values in hsPDA infants early after birth reflect the early relaxant state of ductal muscular tone. ETCOc <2.5 ppm within 24 h after birth may predict the subsequent absence of hsPDA. ETCOc showed no correlation with cerebral oxygenation in both groups

Introduction

Patency of the ductus arteriosus during the prenatal and early neonatal period is a result of intravascular pressure in combination with the action of vasoactive agents, of which prostaglandin E_2 (PGE_2) plays a major role and nitric oxide (NO) and carbon monoxide (CO) have been shown to be additional effectors.[1,2] Formation and action of PGE_2, NO and CO in the modulation of the ductal tone is a complex and changing process during the prenatal period towards term. In the prenatal and preterm infant the ductus is prevented from constriction due to its increased sensitivity to PGE_2 and NO.[1] In addition, in the prenatal lamb, formation of CO in the ductus arteriosus was demonstrated, exerting a relaxing influence on muscle tone and it was postulated that CO, in concert with NO, protects the fetus against ductal closure.[3] The CO-forming enzyme hemoxygenase (HO)-1, expressed both in endothelium and in vascular smooth muscle cells, may be upregulated by noxious stimuli, such as pro-inflammatory cytokines, resulting in relaxation of the ductal wall.[3]

Recently, several clinical studies provided evidence for the importance of these mechanisms in the compromised vascular tone of preterm infants. We have found an association between low blood pressure and CO-mediated increased levels of cyclic guanosine monophosphate (cGMP) in preterm infants with respiratory distress syndrome (RDS).[4] Since cGMP was increased without increased excretion of NO_2^- and NO_3^-, and its levels were only correlated with plasma carboxyhaemoglobin (COHb) concentrations, a causal relationship between endogenous CO production and upregulation of cGMP was considered feasible. It was hypothesized that the increased CO production, as measured by the concentration of COHb, created a state of increased vasodilation of the systemic vascular bed. Further analysis indeed showed an inverse relation between cGMP levels and mean arterial blood pressure, all supportive of the importance of the influence of CO on vascular muscle tone. In addition, a study on microvascular blood flow in preterm infants showed a strong positive correlation between microvascular blood flow and plasma COHb levels.[5]

As an alternative for the measurement of COHb levels in plasma, end-tidal CO, corrected for CO in ambient air (ETCOc) is used as a measure of endogenously produced CO, which after diffusion from endothelial and vascular muscle cells into the bloodstream is transported to the lungs as COHb, diffuses into the alveolar air and is exhaled and can be measured as ETCOc.[6,7] Earlier studies have shown that ETCOc is a useful parameter in the prediction of chronic lung disease[8-10] and adverse neurodevelopmental outcome[11] and it is suggested that ETCOc is associated with inflammation and oxidative stress. Since the majority of preterm infants with severe RDS have a persistent PDA, it is hypothesized that measurement of ETCOc during the first days of life may yield increased levels of ETCOc, indicating increased endogenous CO production, triggered by the RDS-related pro-inflammatory state. In addition, since mean arterial blood pressure values are frequently low during severe RDS compromising the perfusion of the immature brain and CO relaxes vascular muscle tone, including that of the neonatal brain,[12] it is of particular interest to study the relation between ETCOc and cerebral blood flow, as estimated by measuring the regional cerebral oxygen saturation ($rScO_2$) using near-infrared spectroscopy (NIRS).[13] In addition, the value of ETCOc to predict hemodynamically significant patent ductus arteriosus (hsPDA) was studied.

Methods

Clinical parameters

91 infants ≤32 weeks gestational age (GA) admitted to the neonatal intensive care unit of the Wilhelmina Children's Hospital, Utrecht University Medical Center between 2007 and 2009, were studied. Obstetrical and neonatal data were collected prospectively. RDS was graded according to radiographic signs and clinically according to surfactant replacement therapy (SRT) as moderate RDS (no SRT) or severe RDS (SRT). hsPDA was diagnosed based on clinical indices and confirmed by Doppler echocardiographic indices, such as left atrial and/or left ventricular dilatation, internal ductal diameter >1.4 mm/kg and left pulmonary artery end-diastolic flow >0.2 m/s. Peri/intraventricular haemorrhage (PIVH) was diagnosed using cranial ultrasound and graded according to the classification of Papile. A blood pressure support score was used to classify mean arterial blood pressure[14]: 0 = no treatment, 1 = volume expansion and/or dopamine ≤5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, 2 = dopamine >5 to ≤10 $\mu g \cdot kg^{-1} \cdot min^{-1}$, 3 = dopamine >10 $\mu g \cdot kg^{-1} \cdot min^{-1}$, 4 = dopamine and dobutamine >10 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and 5 = additional adrenaline and/or corticosteroids. Treatment of low blood pressure was indicated when the mean arterial blood pressure was below the number of GA in weeks. Blood for routine determinations such as blood gases, glucose, bilirubin, C-reactive protein and hemoglobin (Hb) were sampled via an indwelling arterial catheter. The data were used anonymously, the study was approved by the independent hospital review board and parenteral consent was obtained.

ETCOc

ETCOc was measured within 24 h after birth with a single-use nasal sampler using the $COCO_2$Puff (Everest Biomedical Instruments, Chesterfield, Mo., USA). In infants with spontaneous ventilation the nasal sampler was inserted approximately 5 mm into the

nostril. In case of mechanical ventilation the sampler was inserted into the proximal part of the endotracheal tube via a T-connector.[10] With the $COCO_2$ Puff, a device comparable to the Natus CO-Stat™ End Tidal Breath Analyzer (Natus Medical, Inc., San Carlos, Calif., USA) ETCOc, $ETCO_2$ and ventilatory rate were measured non-invasively at the bedside.[7] The $COCO_2$ Puff contains an infrared CO_2 sensor and an electrochemical CO/hydrogen sensor. The $ETCO_2$ was measured with a resolution of 0.3 or 5% of the reading (whichever is greater) and the ETCOc was measured with a resolution of 0.3 parts per million (ppm) or 10% of the reading. When the $COCO_2$ Puff measured hydrogen concentrations exceeding 50 ppm, above which ETCOc measurement is influenced significantly, the measurement was terminated. ETCOc measurements were performed in duplo and the mean was used for the study. ETCOc values <2.5 ppm were considered to be within the normal range.[10] Since maternal smoking may affect CO concentration in the fetus, infants who were exposed to maternal smoking were excluded from the study. In addition, infants with perinatal infection were also excluded since infection may also influence CO production.[15–18]

Cerebral oxygenation

According to our routine procedure, infants were monitored with NIRS during the first 72 h after birth to determine $rScO_2$ values in order to assess the oxygen delivery to the brain.[13] INVOS 4100/5100 near-infrared spectrometer (Somanetics Corp., Troy, Mich., USA) was used, consisting of a transducer (SAFB-SM Sensor®) containing a light-emitting diode and two distant sensors which were attached to the frontoparietal side of the infant's head. $rScO_2$ was calculated from the differential signals obtained from the two sensors, expressed as the venous-weighted percentage of oxygenated Hb [oxygenated Hb/total Hb (oxygenated + deoxygenated Hb)].[13] For the analysis of the relation with ETCOc and hsPDA, $rScO_2$ values during the period 12-18 h after birth were used, provided that a reliable $rScO_2$ signal was present during at least 50% of that period. If this was not the case, an adjacent 6-hour block was used for the analysis, i.e. between 6 and 12 h after birth, or between 18 and 24 h after birth. Sudden, non-gradual decreasing $rScO_2$ values to below 30% were considered to be artifacts and were removed from the registration. Mean and SD $rScO_2$ values were calculated during the 6-hour period using the Signal Base® program designed at Wilhelmina Children's Hospital Utrecht, the Netherlands.

Statistical analysis

Infants were divided into two groups based on the presence or absence of hsPDA. Data were summarized as mean ± SD or as median and range, where appropriate. A t test or X^2 test was used to compare patient characteristics and differences between the groups. The correlation between ETCOc and NIRS was tested with linear regression analysis. The correlation between ETCOc, Hb and bilirubin was studied with regression analysis. The predictive values of ETCOc for the diagnosis of hsPDA was determined. Statistical analysis was performed using SPSS 15.0.1 for Windows and MedCalc 11.5.0.0 (SPSS/MedCalc, Mariakerke, Belgium). Statistical significance was assumed for $p < 0.05$.

Results

Important clinical characteristics are shown in Table 1. In total, 20/91 infants were diagnosed with hsPDA. Significant differences were found for almost all clinical characteristics: GA was shorter, birth weight was lower, Apgar score at 5 min was lower and the frequency of the diagnosis severe RDS requiring SRT was higher in the hsPDA group, as was the frequency of mechanical ventilation, both for SIMV and HFOV. Antepartum maternal glucocorticoid use was more frequent in the no-hsPDA group. The incidence of PIVH was low and did not differ between groups. Noteworthy, plasma bilirubin levels were significantly higher in the no-hsPDA group. Blood pressure support scores did not differ between the two groups (data not shown).

ETCOc and hsPDA

Figure 1 shows higher values of ETCOc, measured within the first 24 h after birth in the group with hsPDA compared to no-hsPDA (mean ETCOc 2.3 ± 0.7 and 1.7 ± 0.6 ppm, respectively, $p<0.001$). Table 2 shows the predictive values of ETCOc for the diagnosis of hsPDA.

ETCOc and cerebral oxygenation

NIRS-monitored $rScO_2$ values were obtained from 78 of 91 infants, 17/20 in the hsPDA group and 61/71 of the no-hsPDA group. The mean $rScO_2$ values were not significantly different between the two groups (64 ± 1% in hsPDA vs. 65 ± 3% in no-hsPDA).
Figure 2 shows that no correlation could be detected between $rSCO_2$ and ETCOc values ($r^2=0.002$, ns).

Table 1. Clinical characteristics.

Clinical data	No hsPDA	hsPDA	p-value
N	71	20	
GA (mean ± SD)	29.7 ± 1.6	27.7 ± 1.8	< 0.001
BW (mean ± SD)	1,347 ± 360	1,038 ± 274	< 0.01
Apgar 5 min (mediaan, range)	9 (5 – 10)	8 (4 – 9)	< 0.01
Antepartum glucocorticoids, n (%)	63 (89)	14 (70)	< 0.05
Assisted breathing, n (%)			
• Non	25 (35)	1 (5)	< 0.05
• CPAP	35 (49)	6 (30)	ns
• SIMV / HFOV	11 (16)	13 (65)	< 0.001
RDS, n (%)			
• No	45 (63)	5 (25)	< 0.05
• Moderate	9 (13)	0 (0)	ns
• Severe	17 (24)	15 (75)	< 0.001
Hb (mean ± SD)	10.3 ± 1.5	9.5 ± 1.9	ns
Max plasma bilirubin <48h µmol/L (mean ± SD)	125 ± 28	105 ± 27	< 0.01
PIVH, n (%)	8 (75)	1 (5)	ns

Values are mean ± SD, unless indicated otherwise. CPAP: continuous positive airway pressure; HFOV: high frequency oscillatory ventilation; PIVH: perinatal intraventricular haemorrhage present on the first day of life; RDS: respiratory distress syndrome of the newborn; SIMV: synchronized intermittent mandatory ventilation.

Table 2. Predictive values of ETCOc for hsPDA using a cut-off value of 2.5 ppm.

	Yes hsPDA	No hsPDA	
ETCOc high	12	10	PPV 55 %
ETCOc low	8	61	NPV 88 %
	Sensitivity 60 %	Specificity 86 %	

Predictive values of ETCOc for a hemodynamically important patent ductus arteriosus, using a cut-off value of 2.5 PPM. etCOc: end-tidal carbon monoxide corrected for ambient air CO; hsPDA: hemodynamically significant patent ductus arteriosus.

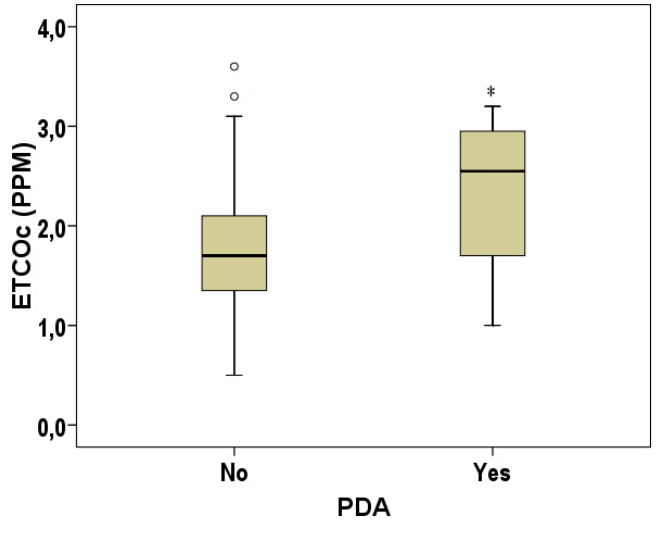

Figure 1. Box-and-whisker plots of ETCOc expressed as ppm in 20 infants with hsPDA and 71 infants without hsPDA. *p<0.001.

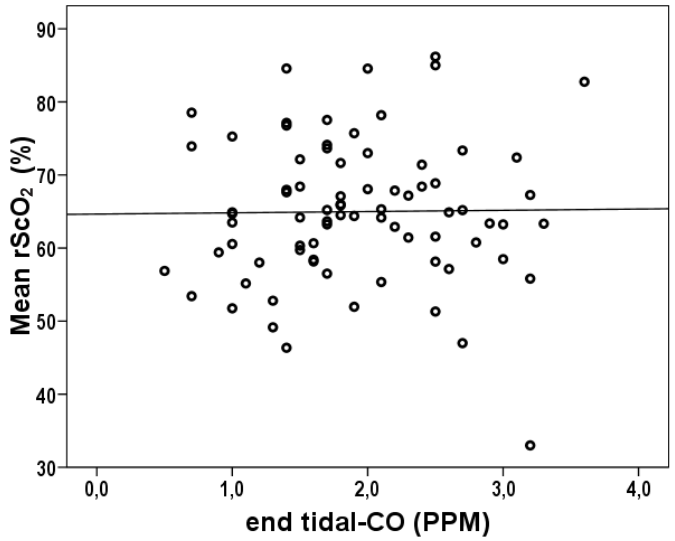

Figure 2. Mean values of NIRS-monitored $rScO_2$ (%) during a 6-hour period and ETCOc values (ppm), measured within 24 h after birth.

Discussion

Preterm infants developing hsPDA had significantly higher ETCOc values measured within 24 h after birth than infants who did not develop hsPDA. However, although the positive predictive value of ETCOc to predict hsPDA within 24 h after birth was only 55%, the high negative predictive value of the parameter (88%) may be used to designate infants who will not develop hsPDA. This knowledge may be useful in the decision to early initiate and increase enteral feedings without the additional risk of intestinal complications due to hsPDA. NIRS-determined $rScO_2$ values during the first 24 h after birth did not correlate with ETCOc. Evaluation of the clinical characteristics revealed that hsPDA developed more frequently in infants with shorter GA, lower birth weight and severe RDS, which is in agreement with the literature.[19] The higher ETCOc values in these infants compared with the values in infants without hsPDA suggest the presence of a vasodilatory circulatory state. Since earlier studies already revealed an association between severe RDS and increased values for ETCOc,[10] it is conceivable that the infants are in a pro-inflammatory state, resulting in preterm birth, severe RDS and development of hsPDA. However, the vasodilatory state could not be confirmed by higher blood pressure support scores in these infants. In addition, since no correlation was found between ETCOc and $rScO_2$ values, ETCOc appeared not to be indicative of cerebral blood flow, although the high ETCOc values might have suggested increased cerebral blood flow due to vasodilation of the cerebral vasculature. However, it is hypothesized that autoregulation of the cerebral arterial vascular bed may already be operative from the first postnatal day neutralizing the vasodilating effects of CO.[20,21] In addition, the vasodilative effect of CO on the cerebral vascular bed may be undetectable due to the hemodynamic changes occurring during the early transitional period.[22] It is of note that earlier studies showed that cerebral blood flow was decreased during the first day of postnatal life and this was associated with the occurrence of IVH.[23]

Several factors may potentially influence ETCOc levels. ETCOc is partly determined by exogenous CO, such as in cigarette smoking, including maternal smoking affecting the fetus, or position in environments with high CO concentration, such as in traffic.[15] We excluded all infants prenatally exposed to maternal smoking. Neonatal intensive care units are not exposed to high CO, and ETCOc measurements were performed within the incubators or inside the endotracheal tube, ruling out the interference of ETCOc by environmental CO. The administration of supplementary oxygen has been shown to affect exhaled CO levels in critically ill adults.[24] However, this effect was seen immediately after an increase in FiO_2 and appeared to be transient. Therefore, increases in FiO_2 were not considered to interfere with the presented ETCOc measurements in our study.

Several other phenomena may cause increased endogenous CO production of which the degradation of heme is an important pathway, resulting in increased production of bilirubin.[6,18] However, we found even lower plasma bilirubin levels in the hsPDA infants who had the higher ETCOc values, suggesting that hemolysis was not a causative pathway in the infants with high ETCOc values in our study. Whether sepsis, being a state of inflammation, may influence ETCOc values has not been reported. However, our study did not include infants with proven early-onset sepsis, ruling out this possibility of interference with ETCOc values.

Conclusion

In conclusion, during the first 24 h after birth, ETCOc values are higher in infants who later develop hsPDA than in infants who do not develop hsPDA, reflecting differences in the early relaxant state of the ductal muscular tone between the two groups. Finding a value of ETCOc<2.5 ppm within the first 24 h after birth may be predictive of the subsequent absence of hsPDA, which is important information for the management of the infant. ETCOc was not correlated with cerebral oxygenation.

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Long-term outcome after patent ductus arteriosus treatment in extremely preterm infants

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Moniek S. Veldhuis[1], Laura M. L. Dix[1]
Johannes M. P. J. Breur[2], Willem B. de Vries[1]
Corine Koopman[1], Inge-Lot C. van Haastert[1]
Renske Schappin[3], Frank van Bel[1]
Petra M. A. Lemmers[1], Daniel C. Vijlbrief[1]

Departments of [1] Neonatology, [2] Pediatric Cardiology and [3] Pediatric Psychology,
Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

To be submitted.

CHAPTER 8

Long-term outcome after patent ductus arteriosus treatment in extremely preterm infants

Abstract

Introduction A hemodynamically significant patent ductus arteriosus (hsPDA) affects almost two-thirds of the neonates born before 28 weeks of gestational age (GA). Although conservative management strategies are increasingly accepted, prolonged ductal patency could be harmful to the preterm brain. To date, studies on long-term outcome after hsPDA treatment are scarce and only reported up to 2 years of age. We hypothesized that a prolonged presence of a hsPDA negatively affects long-term outcome at an early school age.

Methods All infants (GA<28 weeks) with serial echocardiography in the first week of life between 2008 and 2010 were included, and divided into three groups based on hsPDA treatment: indomethacin, surgical ligation, or control group (no treatment). Near-infrared spectroscopy (NIRS) monitored regional cerebral oxygen saturation ($rScO_2$) before echocardiography. Neurodevelopmental outcome (NDO) was assessed at 2 years with the Dutch Bayley Scales of Infant and Toddler Development 3rd Edition (BSITD-III-NL) and at 5 years with the Movement Assessment Battery for Children 2nd Edition (M-ABC-2) and Dutch Wechsler Preschool and Primary Scale of Intelligence 3rd Edition (WPPSI-III-NL). Multivariable logistic regression calculated (adjusted) odds ratios ((a) OR), corrected for peri- and postnatal confounders.

Results 78 infants were included. NDO at 2 years of age was available for 70 (89.7%) infants. No differences were found in death or poor NDO (BSITD-III-NL<1SD) between the 3 groups. At 5 years of age, motor performance was assessed in 65 (83.3%) infants. Poor motor outcome (M-ABC-2; PS<5) occurred more often in hsPDA treated infants but was not significant in multivariate analysis. Cognition was tested in 56 (71.8%) infants. hsPDA surgery was a significant risk factor for poor cognitive outcome (WPPSI-III-NL<1SD) (aOR: 17.15, 95% CI: 1.21-242.17; p: 0.03). $rScO_2$ was significantly lower in infants with a poor cognitive outcome (mean±SD: 54.2±6) compared to infants with a good cognitive outcome (61.6±7; p: 0.003).

Conclusion hsPDA surgery is significantly related to impaired cognitive function at early school age, potentially due to suboptimal cerebral oxygenation. NIRS-monitoring of cerebral oxygenation might identify infants at risk for poor NDO.

Introduction

A hemodynamically significant patent ductus arteriosus (hsPDA) affects almost two-thirds of the neonates born before 28 weeks of gestational age (GA).[1,2] The left-to-right ductal shunt can cause a diminished perfusion of the systemic circulation with an excessive pulmonary flow.[3] This ductal steal phenomenon also affects the neonatal brain.[4,5] A hsPDA has been associated with increased mortality as well as serious morbidities, such as bronchopulmonary dysplasia (BPD), peri-intraventricular haemorrhage (PIVH), and necrotising enterocolitis (NEC).[6-10] Even though a causal relation has not yet been determined, evidence cannot support the conclusion that ductal patency is safe.[11,12]

A hsPDA negatively affects cerebral perfusion and oxygenation through ductal shunting, as well as by a duct-induced reduction in blood pressure.[13] Infants requiring surgical ductal ligation are more severely affected.[13,14] Prolonged suboptimal cerebral oxygenation has been related to cerebral injury and impaired growth of the cerebellum.[15-18] When a hsPDA is not treated, exposure to adverse cerebral perfusion and oxygenation may be prolonged. This applies especially to extremely preterm infants, as they show delayed spontaneous closure of their duct.[19,20]

The decision whether or not to treat a hsPDA remains a topic of debate. Although a hsPDA is associated with several neonatal complications, recent literature suggests that active treatment of a hsPDA may also be harmful. A potential association has been suggested between cyclooxygenase inhibitors and increased risk of intestinal perforation and BPD.[21,22] Infants who need surgical ligation develop BPD and retinopathy of prematurity more often, and are prone to complications related to the surgical procedure such as vocal cord paresis and pneumothorax.[23-25] Therefore, conservative management strategies are increasingly accepted.

Evidence on long-term neurodevelopmental outcome (NDO) after hsPDA treatment could facilitate the decision whether or not to treat. Unfortunately, studies are scarce, and outcome has only been reported up to 2-3 years of age.[26,27] Determining neurological outcome at (pre-)school age would be of particular interest since subtle differences in higher cognitive functions, not apparent at an earlier age, can be distinguished at this age. In this study, we assessed hsPDA treatment, cerebral oxygenation, and NDO at 2 years and 5 years of age in preterm infants born before 28 weeks of gestation. Our hypothesis states that a hsPDA with low cerebral oxygenation negatively affects long-term NDO.

Methods

Patients

This retrospective observational study is a subgroup analysis of a previously published prospective cohort study from 2016, analysing the association between cerebral oxygenation and echocardiographic parameters in preterm infants (<32 weeks GA) with and without a hsPDA.[28] From the original cohort of 380 preterm infants, 78 extremely preterm infants (<28 weeks GA) could be selected. Peri- and postnatal characteristics were collected from hospital records. PIVH was graded by the classification of Papile.[29] Follow-up data was retrospectively obtained from our standard follow-up program for all preterm infants with a GA below 28 weeks. The study was approved by the medical ethical committee of the University Medical Center Utrecht, and informed consent was waived as data was provided anonymously by the treating physician in accordance with Dutch law.

hsPDA

As part of the prospective cohort study, three echocardiographic examinations were performed during the first week of life by a paediatric cardiologist.[28] Results were blinded for the attending neonatologist. When clinical suspicion of hsPDA arose, the ultrasound results were unblinded. An open duct was considered haemodynamically significant if one or more of the following criteria were confirmed by echocardiography, (a) ductal diameter >1.4mm, (b) presence of growing or pulsatile ductal flow pattern, (c) left pulmonary artery-end diastolic flow>0.2 m/second, and (d) left atrial to aortic root ratio >1.4 mm.[30,31]

Treatment decisions for hsPDA were made by attending neonatologists. Indomethacin was the primary treatment option and included three successive intravenous doses of 0.2 mg/kg every 12 hours, provided that there were no contraindications. A second course of indomethacin was prescribed when the duct appeared to be responsive but was not yet fully closed. Surgical ligation was performed when indomethacin was contraindicated, or when the hsPDA failed to close after medical intervention. Infants were divided into three groups based on their hsPDA treatment: (1) preterm infants who did not receive hsPDA treatment (NoTREAT), (2) infants who were treated with indomethacin (MED) and (3) infants who underwent surgical ligation for their hsPDA (SURG).

Cerebral oxygenation

Regional cerebral oxygen saturation ($rScO_2$) was monitored with the INVOS 5100C near-infrared spectroscopy (NIRS) monitor (Medtronics, Minneapolis, MN) and the small adult sensor (SomaSensor SAFB-SM, Covidien, Mansfield, MA) during at least one hour prior to each echocardiographic examination during the first week of life, according to study protocol.[28] The NIRS sensor was attached to the fronto-parietal side of the infants' head. Cerebral oxygenation monitoring for at least 72 hours after birth or longer if indicated is standard clinical care in our neonatal intensive care unit (NICU) for all preterm infants born <30 weeks GA. A representative period of one hour stable cerebral monitoring was selected before cardiac ultrasound. In the NoTREAT group, a similar period was selected prior to the second ultrasound as a comparison. In addition, postnatal age (PNA) at treatment of hsPDA and duration until hsPDA closure were recorded.

Neurodevelopmental assessment at 2 years of age

All extremely preterm infants are routinely invited for follow-up assessment at 30 months of age in our NICU. NDO was assessed by certified investigators using the Dutch version of the Bayley Scales of Infant and Toddler Development, Third Edition (BSITD-III-NL), which is standardized for the Dutch population.[32,33] The BSITD-III-NL entails a cognitive score and a motor score consisting of both fine- and gross-motor skills. Language scores were not included in this study since they were not routinely assessed in our follow-up program. Poor outcome was defined as a cognitive- or motor score <1 standard deviation (SD) (<85). In addition, a composite score of death or a poor NDO was analysed.

Neurodevelopmental assessment at 5 years of age

NDO evaluation was repeated at 5 years of age, as part of standard care. Motor performance was assessed with the Movement Assessment Battery for Children, Second Edition (M-ABC-2) by a paediatric physiotherapist.[34,35] The M-ABC-2 consists of eight scoring items evaluating three different domains: manual dexterity (three items), aiming and catching (two items) and balance (three items), of which a total test score is calculated. Based on percentile scores (PS) of the total test score, three different categories can be distinguished: normal motor function (PS≥15), borderline motor impairment (5<PS<15), and significant motor impairment (PS<5). The last category was defined as poor motor outcome in our study. The M-ABC-2 test scores were interpreted according to the specified norms for the Dutch population. Cognition was evaluated at a separate visit by a paediatric psychologist with the Dutch version of the Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III-NL).[36] The WPPSI-III-NL measures verbal- and

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performance intelligence quotient (IQ), which are combined to determine a full-scale IQ. Each scale has a mean score of 100 with a SD of 15. Cognitive outcome was defined as poor when the full-scale IQ-score was below 1 SD (<85).

Statistical analysis

Data are presented as means (±SD), as medians (range or interquartile range (IQR)), or as count (percentage), where appropriate. Clinical characteristics, cerebral oxygenation values, and NDO were compared between the three groups with the Chi-Square test and analysis of variance (ANOVA) or the Kruskal-Wallis-test in case of non-parametric data. Comparison between good and poor outcome was analysed with independent samples T-test or the Mann-Whitney U test. Logistic regression analysis was used to calculate the (adjusted) odds ratios (OR) with a 95% confidence interval (CI) for poor NDO. Potential cofounders included respiratory support, postnatal steroid use for BPD, inotropic support, and severe PIVH (grade 3 or 4 according to the classification by Papile).[29] To calculate odds ratio's the treated infants, MED and SURG, were combined into one group (TREAT) and compared to the infants without treatment (NoTREAT) since the SURG group alone was too small for logistic regression. The effect of surgical ligation on NDO was assessed by including this variable as a separate covariate. All covariates were introduced in logistic regression by block-wise entry. A p-value of <0.05 was considered statistically significant. All analyses were performed using SPSS for Windows (IBM Statistics SPSS version 23).

Results

Patients

Clinical characteristics are shown in Table 1. Of the 78 infants, 38 did not develop a hsPDA (NoTREAT) and 40 infants were treated for a hsPDA: 29 in the MED group and 11 in the SURG group. Six infants were immediately surgically ligated due to contraindications for indomethacin. Mean PNA at closure was 7.0±3.14 days. Infants who developed a hsPDA were sicker than infants without a hsPDA, with significantly more respiratory and inotropic support and postnatal steroids. In addition, hsPDA-treated infants had higher rates of severe PIVH (grade 3 or 4), most pronounced in the SURG group (Table 1). No differences were found in ductal characteristics between MED and SURG group (Supplemental Table 1). Two infants developed a vocal cord paresis after ductal surgery. Follow-up analysis inclusions are shown in Figure 1.

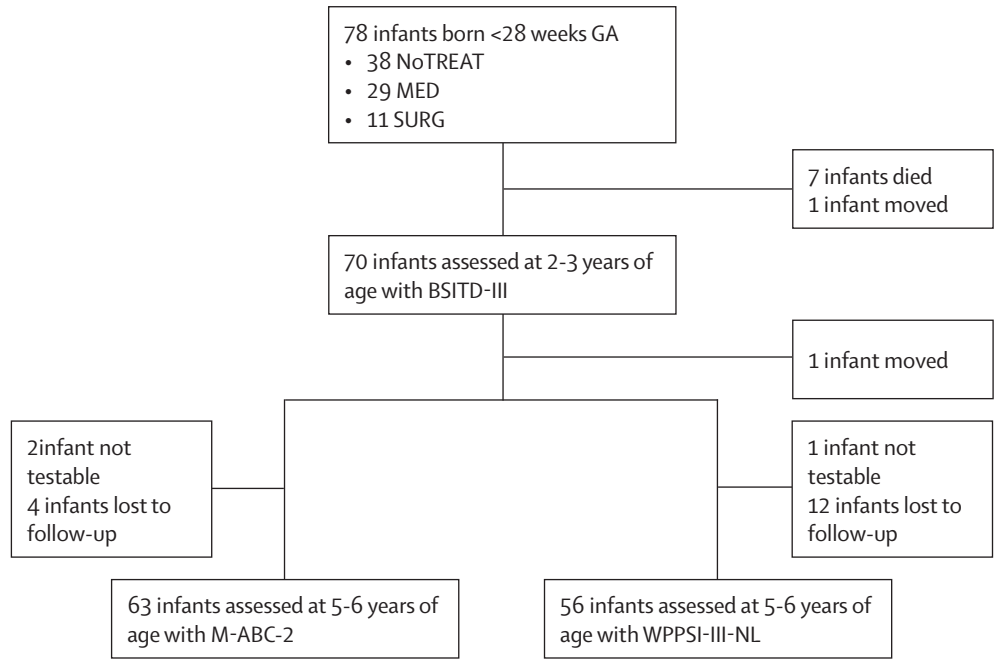

Figure 1. Flowchart of inclusions.

NDO at 2 years of age

NDO was tested in 70 (89.7%) infants. The 7 infants who died all passed away before one month of age: 4 infants due to severe respiratory complications, 1 infant from a perforated NEC and 2 infants had a fatal neurological prognosis. Mean corrected age at testing was 29.8±1.7 months. No differences were found in death or poor NDO between the three groups and the OR comparing treated versus non-treated infants was not significant. See Table 2. Ductal surgery and severe PIVH were related to NDO at 2 years of age in multivariate analysis and were introduced as confounding factor. Respiratory support, postnatal steroids for BPD, and inotropic support were not related and excluded from further analysis. Severe PIVH and surgery for hsPDA had a negative effect on the outcome, although not significant as shown in Table 3. Sub-scores of the BSITD-III-NL are shown in Supplemental Table 2. None of the infants suffered from hearing loss, bilateral blindness, or cerebral paresis. Infants with a good outcome did not differ from infants in the death or poor NDO group with regards to $rScO_2$ before hsPDA treatment (61.1±7.6 vs. 61.3±9.0, respectively). PNA at diagnosis or PNA at closure was not related to death or poor outcome (data not shown).

Table 1. Neonatal characteristics.

	NoTREAT n=38	MED n=29	SURG n=11	p-value
Male gender	20 (52.6)	17 (58.6)	9 (81.8)	0.23
Gestational age (week), mean±SD	26.8±0.9	26.6±1.0	26.1±1.1	0.15
Birth weight (g), mean±SD	929±153	861±184	990±207	0.08
Apgar 1 min, median (range)	5 (1-9)	5 (0-9)	5 (1-8)	0.80
Apgar 5 min, median (range)	8 (5-10)	7 (4-9)	7 (3-9)	0.23
aCCS full course	34 (89.5)	21 (72.4)	9 (81.8)	0.17
Respiratory support during 7 days after birth • Not intubated (none, low flow, CPAP) • Intubated (SIMV, HFO)	 9 (23.7) 29 (76.3)	 0 (0) 29 (100)	 0 (0) 11 (100)	0.004
IRDS with surfactant	23 (60.5)	24 (82.8)	10 (90.9)	0.05
Sepsis	11 (28.9)	10 (34.5)	6 (54.5)	0.29
Severe PIVH	2 (5.3)	5 (17.2)	4 (36.4)	0.003
Postnatal steroid use for BPD	6 (15.8)	7 (24.1)	6 (54.5)	0.04
Inotropic support	15 (39.5)	19 (65.5)	8 (72.7)	0.04
Mortality	2 (5.3)	4 (13.8)	1 (9.1)	0.42

Data are n (%) unless otherwise specified. aCCS: antenatal corticosteroids; BPD: bronchopulmonary dysplasia; CPAP: continuous positive airway pressure; SIMV: synchronized intermittent mandatory ventilation; HFO: high-frequency oscillatory ventilation; IRDS: infant respiratory distress syndrome; severe PIVH: periventricular- or intraventricular haemorrhage grade 3 or grade 4 according to Papile.[29]

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NDO at 5 years of age

Motor performance analysis was completed in 63 infants with the M-ABC-2 test. Seven infants were lost to follow-up, none of which were deceased (see Figure 1). Mean age at testing was 70.1±2.7 months. No relevant differences in perinatal characteristics were found between the group with NDO assessments and the infants lost to follow-up (Supplemental Table 3). Infants from both the MED and SURG group showed higher rates of poor motor outcome compared to infants in the NoTREAT group, as shown in Table 2. No association was found between hsPDA treatment or ductal surgery in multivariate analysis as shown in Table 3. Sub-scores of the M-ABC-2 are shown in Additional Table 4.

Table 2. Unadjusted odds ratios neurodevelopmental outcome.

Age	Outcome	NoTREAT	MED	SURG	p-value	OR# [95% CI]
2 yr n=16/77	Death or poor NDO (<1SD BSITD-III-NL)	8/37 (21.6)	5/29 (17.2)	3/11 (27.3)	ns	0.91 [0.30-2.73]
5 yr n=11/63	Poor motor outcome (PS<5 M-ABC-2)	2/32 (6.3)	4/22 (18.2)	5/9 (55.6)	0.004	6.14 [1.21-31.26]
5 yr n=11/56	Poor cognitive outcome (<1 SD WPPSI-III-NL)	5/27 (18.5)	2/20 (10.0)	4/9 (44.4)	0.84	1.15 [0.31-4.31]

Results in n (%). #TREAT (MED and SURG) vs NoTREAT group, unadjusted.

Infants with a poor motor outcome had lower $rScO_2$ values (54.4±8) compared to infants with a good outcome (61.2±7). However, this difference was not significant (p:0.103). PNA at diagnosis or PNA at closure was not related to a poor motor outcome (data not shown).

Cognitive assessment was completed in 56 infants. Fourteen infants were lost to follow-up (see Figure 1). No relevant differences were found between infants who were tested with the WPPSI-III-NL and those lost to follow-up (Supplemental Table 3). Mean age

Table 3. Adjusted odds ratios neurodevelopmental outcome.

Age	Neurodevelopment outcome	Adjusted OR [95%CI]	p-value
2 yr	Death or poor NDO (<1SD BSITD-III-NL)		
	• TREAT	0.72 [0.20-2.53]	0.60
	• Severe PIVH	1.50 [0.32-7.11]	0.61
	• Surgery hsPDA	1.66 [0.31-8.86]	0.55
5 yr	Poor motor outcome (PS<5 M-ABC-2)		
	• TREAT	2.67 [0.42-17.06]	0.30
	• Severe PIVH	5.19 [0.79-33.98]	0.09
	• Surgery hsPDA	4.76 [0.79-28.79]	0.09
5 yr	Poor cognitive outcome (<1 SD WPPSI-III-NL)		
	• TREAT	0.63 [0.09-4.13]	0.63
	• Severe PIVH	1.64 [0.07-39.84]	0.76
	• Surgery hsPDA	17.15 [1.21-242.17]	0.03
	• Inotropic support	0.05 [0.05-0.66]	0.02

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at testing was 70.4±4.1 months. On multivariate analysis, surgery for hsPDA was significantly related to a poor cognitive outcome. Use of inotropic support in the neonatal period was significantly related to good cognitive outcome. See Table 3. Sub-scores of the WPPSI-III-NL are shown in Supplemental Table 5. $rScO_2$ in % prior to treatment was significantly lower in infants with a poor cognitive outcome compared to a good cognitive outcome as shown in Table 4. Postnatal age in days at start of hsPDA treatment was higher in infants with a poor compared to a good cognitive outcome (5.5±3.5 vs. 3.7±2.4, respectively), although this was not significant. PNA at closure did not differ between groups.

Table 4. Cerebral oxygenation and neurodevelopmental outcome.

Age	$rScO_2$ (%)	Poor outcome	Good outcome	p-value
2 yr	BSITD-III-NL	61.3±9	61.1±7.6	0.373
5 yr	M-ABC-2	54.4±7.6	61.2±7.3	0.103
5 yr	WPPSI-III-NL	54.2±5.6	61.6±7.3	0.003

$rScO_2$: regional cerebral oxygen saturation.

Discussion

Neonatal ductal surgery negatively affects cognitive outcome at 5 years of age in preterm infants. Moreover, cerebral oxygenation is significantly lower in infants with a poor cognitive outcome. A higher incidence of poor motor outcome occurs in infants with ductal treatment. However, these results do not sustain in multivariate analysis. No association was found between death or poor NDO at 2 years and ductal treatment. Research on NDO at pre-school age following hsPDA (and treatment) was, to the best of our knowledge, not yet available. Our study, therefore, provides new insights and leads to a better understanding of long-term effects of a hsPDA.

The effect of hsPDA on NDO has mainly been studied at 2 years of age.[26,27,37,38] In contrast to previous literature, a negative effect of ductal treatment on NDO at 2 years could not be confirmed in our study. The study of Janz-Robinson et al. included 1473 preterm infants, born <29 weeks GA, and reported an independent association between both medical and surgical hsPDA treatment with a poor NDO.[26] Poor NDO was defined as developmental delay on the Bayley Scales of Infant Development, Second Edition, or the Griffiths Mental Development Scale General Quotient, cerebral palsy, deafness or bilateral blindness.

However, this study did not adjust for postnatal covariates, such as PIVH. Bourgoin et al. evaluated 857 preterm infants and found a similar negative effect of ductal surgery on NDO.[27] These differences could be due to our small patient groups. However, Weisz et al. also found no association between surgical ligation and a poor neurodevelopmental outcome after adjustment for postnatal confounders in 680 infants <28 weeks GA.[39] Treatment is initiated early in case of a hsPDA in our centre, which might have a protective effect on NDO at 2 years of age. Moreover, the infants with surgical closure of the duct were the sickest which led to the correction of several confounders.

There are several potential explanations for the obtained adverse cognitive outcome after ductal surgery at 5 years of age. A longer ductal patency in this specific group could be a contributing factor. Our results showed that infants with a poor cognitive outcome tended to receive effective treatment at a later postnatal age. They might be longer exposed to ductal shunting with adverse cerebral oxygenation, as cerebral oxygenation was significantly lower in infants with a poor outcome.

The left-to-right ductal shunt negatively affects $rScO_2$, which normalizes after ductal closure.[13] Even with our early treatment strategy, cerebral oxygenation was significantly lower in infants with a poor NDO. We found a negative effect on NDO at 5 years of age in spite of the relatively short exposure to adverse cerebral oxygenation. Previous research has found an association between low levels of cerebral oxygenation and poor outcome.[17,40] Our group has recently shown an association between low $rScO_2$ before hsPDA closure and reduction in cerebellar growth.[18] Additionally, Padilla et al showed a significant reduction in global and regional brain volumes, predominantly cerebellar, after surgery for hsPDA.[41]

The neonatal brain seems at an increased risk of injury during ductal surgery, as this was an independent risk factor for poor NDO. Previous research has shown that both the surgical procedure and the anaesthetics are potentially harmful in neonates.[42-44] Additionally, cerebral oxygenation is further impaired in infants who require ductal surgery. Lemmers et al. showed that cerebral oxygenation was even lower in the pre-clipping period, remained low during the first hours after ductal clipping and normalised to expected values just 24 hours after completion of surgery.[14] A suboptimal haemodynamic condition with ductal shunting, the effects of anaesthetics, the procedure itself, and the low cerebral oxygenation are all potential contributing factors.

The influence of cerebral oxygenation has not been evaluated in studies regarding NDO after hsPDA. Our results showed an association between impaired cognitive function at early school age and compromised cerebral oxygenation prior to ductal treatment, strengthening the suggestion that long-standing hypoxia may contribute considerably to an adverse NDO. Preventing prolonged ductal patency might improve cerebral oxygenation, and prevent cerebral injury affecting cognitive function. Previous research has shown that cerebral oxygenation monitoring by NIRS with a treatment protocol can stabilize cerebral oxygenation and reduce the burden of hypoxia.[45]

Our study corrected for postnatal covariates in multivariable analyses, which limits the risk of bias due to confounding by indication. However, the small study population, especially in the SURG group, are an important limitation of this study. Although this is a relatively small sample size, we still found a significant effect of ductal surgery and cerebral oxygenation on NDO at 5 years of age.

Conclusion

Our results suggest that surgery for hsPDA is significantly related to an adverse cognitive outcome at early school age. Prolonged exposure to a suboptimal cerebral oxygenation is a potential contributing factor. The use of NIRS-monitoring of cerebral oxygenation might identify infants at risk for adverse NDO. Future research should assess whether active treatment and prevention of low cerebral oxygenation may prevent long-standing cerebral hypoxia, and potentially improve cognitive outcome at long-term follow-up.

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Supplemental material

Supplemental Table 1. Ductal characteristics.

	MED n= 29	SURG n= 11	p-value
Age at treatment (days)	2 (1-8)	3 (1-10)	0.34
Age at closure (days)	7 (3-14)	6 (2-12)	0.83
Ductal diameter (mm) mean±SD (mm)	1.96±0.11	1.99±0.10	0.89
Left atrium : Aorta ratio	1.7 (1.4-2.5)	1.6 (1.4-2.3)	0.07
Courses of indomethacin	2 (1-3)	0 (0-3)	0.02

Results in median (range) unless otherwise specified. PNA: postnatal age.

Supplemental Table 2. Neurodevelopmental outcome at 2 years of age assessed with BSITD-III-NL.

	NoTREAT n= 35	MED n= 25	SURG n=10	p-value
Corrected age at testing (months), mean±SD	29.78 ±1.88	29.66 ±1.80	30.25 ±0.50	0.68
Cognitive Composite Score	96.00 [14.00]	101.00 [28.00]	96.00 [20.50]	0.41
Motor Composite Score	107.00 [27.50]	109.00 [18.50]	101.00 [20.00]	0.43
Gross Motor Scaled Score	9.50 [4.50]	10.00 [4.75]	9.00 [4.00]	0.58
Fine Motor Scaled Score	11.00 [5.25]	12.50 [3.50]	11.00 [5.50]	0.21
Poor outcome (BSITD-III-NL<1SD), n (%)	6 (17.1)	2 (7.7)	1 (11.1)	0.63

Results in median [IQR] unless otherwise specified.

Supplemental Table 3. Lost to follow-up analysis for assessment at 5 years of age.

	M-ABC-2			WPPSI-III-NL		
	Lost to FU n=7	Included FU n= 63	p-value	Lost to FU n=14	Included FU n= 56	p-value
Male gender	5 (71.4)	39 (61.9)	1.00	10 (71.4)	34 (60.7)	0.46
GA (wk), median [IQR]	27.6 [0.4]	26.7 [1.7]	0.01	27.4 [1.1]	26.6 [0.8]	0.02
BW (g), median [IQR]	920 [270]	920 [240]	0.78	932 [245]	920 [263]	0.74
Apgar 1 min, median (range)	2 (1-8)	5 (0-9)	0.31	3 (0-8)	5 (1-8)	0.11
Apgar 5 min, median (range)	7 (3-9)	8 (4-10)	0.25	7 (3-9)	8 (4-10)	0.45
aCCS full course	3 (42.9)	55 (87.3)	0.01	7 (50.0)	51 (91.1)	0.01
Intubated	7 (100.0)	54 (85.7)	0.58	12 (85.7)	49 (87.5)	1.00
IRDS, with surfactant	6 (85.7)	43 (68.3)	0.67	11 (78.6)	38 (67.9)	0.53
Sepsis	1 (14.3)	24 (38.1)	0.41	2 (14.3)	23 (41.1)	0.07
Severe PIVH	1 (14.3)	7 (11.1)	1.00	1 (7.1)	7 (12.5)	1.00
Postnatal steroids for BPD	3 (42.9)	13 (20.6)	0.34	3 (21.4)	13 (23.2)	1.00
Inotropic support	3 (42.9)	34 (54.0)	0.70	7 (50.0)	30 (53.6)	0.81

Results in n (%) unless otherwise specified. GA: gestational age; BW: birthweight; aCCS: antenatal corticosteroids; IRDS: infant respiratory distress syndrome; PIVH: periventricular- or intraventricular haemorrhage; BPD: bronchopulmonary dysplasia; FU: follow-up.

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Supplemental Table 4. Neurodevelopmental outcome at 5 years of age assessed with M-ABC-2.

	NoTREAT n= 32	MED n= 22	SURG n= 9	p-value
Age at testing (months), mean±SD	69.93±3.15	70.39±2.01	69.83±2.26	0.80
Percentile Score Manual Dexterity	25.00 [28.00]	16.00 [58.00]	5.00 [4.25]	0.002
Percentile Score Aiming and Catching	31.00 [31.75]	16.00 [20.00]	7.00 [17.75]	0.01
Percentile Score Balance	37.00 [41.00]	31.00 [51.25]	5.00 [36.00]	0.08
Total Percentile Score	16.00 [31.00]	12.50 [32.00]	2.00 [4.25]	0.001

Results in median [IQR] unless otherwise specified.

Supplemental Table 5. Cognitive outcome at 5 years of age assessed with WPPSI-III-NL.

	NoTREAT n= 27	MED n= 20	SURG n= 9	p-value
Age at testing (months)	69.37 ±5.16	71.50 ±2.33	71.03 ±2.58	0.18
Verbal IQ	96.19 ±14.29	99.75 ±13.85	98.22 ±11.57	0.68
Performance IQ	100.81 ±13.07	100.10 ± 11.39	92.67±14.73	0.25
Total IQ	96.41 ±13.25	99.10 ±12.37	92.89 ±15.11	0.50

Results in mean±SD. IQ: intelligence quotient.

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PART 3

CARBON DIOXIDE

Carbon dioxide fluctuations are associated with changes in cerebral oxygenation and electrical activity in infants born preterm

Laura M. L. Dix, Lauren C. Weeke
Linda S. de Vries, Floris Groenendaal
Willem Baerts, Frank van Bel
Petra M. A. Lemmers

Department of Neonatology, Wilhelmina Children's Hospital
University Medical Center Utrecht, Utrecht, The Netherlands

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CHAPTER 9

Carbon dioxide fluctuations are associated with changes in cerebral oxygenation and electrical activity in infants born preterm

Abstract

Objective To evaluate the effects of acute arterial carbon dioxide partial pressure changes on cerebral oxygenation and electrical activity in preterm infants.

Methods This retrospective observational study included ventilated preterm infants with acute fluctuations of continuous end-tidal CO_2 ($etCO_2$), as a surrogate-marker for arterial carbon dioxide partial pressure, during the first 72 hours of life were included. Regional cerebral oxygen saturation and fractional tissue oxygen extraction were monitored with near-infrared spectroscopy. Brain activity was monitored with 2-channel electroencephalography. Spontaneous activity transients (SAT) rate (SATs/min) and interval between SATs (in seconds) were calculated. Ten minute periods were selected for analysis: before, during, and after $etCO_2$ fluctuations of ≥5mmHg.

Results 38 patients (mean±SD GA 29±1.8 weeks) were included, with 60 episodes of $etCO_2$ increase and 70 episodes of $etCO_2$ decrease. During $etCO_2$ increases, brain oxygenation increased (regional cerebral oxygen saturation increased, fractional tissue oxygen extraction decreased; $p<0.01$) and electrical activity decreased (SATs/min decreased, interval between SATs increased; $p<0.01$). All measures recovered when $etCO_2$ returned to baseline. During $etCO_2$ decreases, brain oxygenation decreased (regional cerebral oxygen saturation decreased, fractional tissue oxygen extraction decreased; $p<0.01$) and brain activity increased (SATs/min increased, $p<0.05$), also with recovery after return of $etCO_2$ to baseline.

Conclusion An acute increase in $etCO_2$ is associated with increased cerebral oxygenation and decreased brain activity, whereas an acute decrease is associated with a decreased cerebral oxygenation and slightly increased brain activity. Combining continuous CO_2 monitoring with near-infrared spectroscopy may enable detection of otherwise undetected fluctuations in arterial carbon dioxide partial pressure that may be harmful to the neonatal brain.

Introduction

Although survival rates are increasing, there is a high rate of morbidity in preterm infants.[1] Cerebral injury acquired in the neonatal period can have a large impact on quality of life. Disturbances in cerebral perfusion and oxygenation can contribute to brain injury in preterm infants and are associated with impaired neurodevelopmental outcome.[2-4]

Changes in arterial carbon dioxide partial pressure (pCO_2) directly affect cerebral perfusion.[5] Hypercapnia induces vasodilation and hypocapnia induces vasoconstriction of the cerebral arterial blood vessels in newborn infants. To what extent this mechanism is operational in the very preterm infant has not been clarified fully. However, the brain of infants born preterm is susceptible to disturbances in flow owing to relatively immature cerebral vascularisation and limited autoregulatory capability.[6]

Abnormal pCO_2 levels have been associated with neuropathology.[7,8] Hypercapnia increases cerebral blood flow with risk of intraventricular haemorrhage (IVH) and periventricular haemorrhagic infarction. Hypocapnia-induced vasoconstriction can lead to ischemic white matter injury. Recent research has shown that fluctuations in CO_2 are also related to severe IVH and increase the risk of neurodevelopmental impairment or death.[7,9]

Fluctuations in pCO_2 are common in ventilated infants and are often caused by respiratory variations. CO_2 fluctuations during continuous end-tidal CO_2 ($etCO_2$) monitoring may not be detected by intermittent arterial pCO_2 analysis. $EtCO_2$ shows a good correlation with pCO_2 and can, within certain limits, be monitored continuously in ventilated infants.[10-13]

Our study aimed to analyse the effects of $etCO_2$ fluctuations, as a surrogate for arterial pCO_2, on oxygenation and electrical activity of the brain. Our hypothesis was that acute increases in pCO_2 cause vasodilatation which in turn might increase cerebral oxygenation and reduce electrical brain activity. Acute decreases in pCO_2 result in vasoconstriction and might decrease cerebral oxygenation and increase activity.

Methods

This retrospective observational study included patients from the neonatal intensive care unit at the Wilhelmina Children's Hospital in Utrecht, The Netherlands. Infants were selected from our cohort of very preterm infants (<32 weeks of gestation) born between October 2009 and January 2016 if they were ventilated with continuous $etCO_2$ monitoring in combination with neuromonitoring during the first three days after birth. Obstetric, intrapartum, and neonatal data were collected from hospital patient records. All clinical decisions were made by the attending neonatologist based on current treatment protocols. The target range of pCO_2 was between 40 and 50 mmHg in ventilated infants. Moderate-to-severe respiratory distress syndrome (RDS) was defined by radiographic features and the need for surfactant therapy. Physiological parameters were monitored with the Philips patient monitor (IntelliVue MP70, Philips, Best, The Netherlands) and included arterial oxygen saturation (SaO_2) with a pulse oximeter, heart rate (HR), and arterial blood pressure (MABP) with an indwelling arterial catheter. Germinal matrix haemorrhages and IVH were diagnosed with cranial ultrasound and graded according to the classification of Papile et al.[14] The diagnosis of a hemodynamically significant patent ductus arteriosus (PDA) was based on clinical symptoms and confirmation by cardiac ultrasound imaging. This study was approved by the Utrecht University Medical Center ethical committee. Parental consent was waived because of the retrospective observational and noninterventional design.

Study design

The $etCO_2$ was monitored in exhaled air in intubated infants with the Philips Intellivue monitor as a surrogate of arterial pCO_2. Acute $etCO_2$ fluctuations were defined as an increase or a decrease of at least 5 mmHg lasting less than 1 hour, with simultaneous neuromonitoring. The $etCO_2$ signals were manually reviewed and automatically verified to identify acute fluctuations. During each acute $etCO_2$ fluctuation in the first 72 hours after birth, a 10 minute period of stable data was selected. We selected $etCO_2$ increases or decreases of at least 10 minutes and not longer than 1 hour to avoid analysing chronic hypercapnia or hypocapnia. A 10 minute control period was selected within approximately 1 hour before the change in $etCO_2$ and after the return of $etCO_2$ to baseline.

Neuromonitoring included continuous assessment of cerebral oxygenation and electrical activity during the first 72 hours after birth, which is standard clinical practice in our neonatal intensive care unit for all infants born before 32 weeks of gestation and in all infants with signs of asphyxia, seizures, in case of suspected congenital anomalies and during neonatal surgery. Regional cerebral oxygen saturation ($rScO_2$) and fractio-

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nal tissue oxygen extraction (FTOE, (SaO_2 – $rScO_2$)/ SaO_2) were monitored by Near-infrared spectroscopy (NIRS) with the INVOS spectrometer (INVOS 5100C, Medtronic, Minneapolis, MN, USA) with a small adult sensor (small adult SomaSensor SAFB-SM, Covidien, Mansfield, Massachusetts).[15] Adult sensors were used because neonatal sensors measure on average 10% higher than the adult sensors, thus losing variability in the higher regions.[16] Electrical activity was monitored by 2-channel (F3-P3, F4-P4) electroencephalography (EEG) with the BrainZ monitors (Natus, Seattle, Washington). The cross-cerebral (P3-P4) 256Hz raw EEG signal was used to calculate the spontaneous activity transients (SAT) rate per minute (SATs/min) and the length of the interval between SATs, the interSATinterval (ISI), in seconds with a non-linear energy operator in the Signal Base software.[17] The EEG signal consists of periods of activity alternated with periods of inactivity, corresponding to a discontinuous background activity, where decreased SAT rate and increased ISI reflect a neurodepressant state.[18]

Statistical analysis

Signal processing was performed with in-house developed software SignalBase (University Medical Center Utrecht, NL). Artefacts were manually removed. Ten-minute periods of stable monitoring before, during, and after $etCO_2$ fluctuations were analysed with repeated measures ANOVA with the Greenhouse-Geisser correction if needed, or Friedman's ANOVA in case of nonlinear data. Linear mixed effects model analysis assessed the association between $etCO_2$ and neuromonitoring variables with a random intercept per patient and $etCO_2$ as the independent variable. The effect of $etCO_2$ was analysed both as a fixed categorical predictor (periods before, during, and after $etCO_2$ fluctuation), as well as a continuous predictor ($etCO_2$ values). With $etCO_2$ as a categorical predictor, the reference category (constant) was the baseline period before the $etCO_2$ fluctuation. Dependent variables of cerebral oxygenation were $rScO_2$ and FTOE, with an additional fixed effect for PDA. Dependent variables of cerebral functioning measures were SATs per min and ISI, with additional fixed effect for morphine. Gestational age (GA), postnatal age, and vital parameters HR, MABP, and SaO_2 were included in all analyses. $P<0.05$ was set to statistical significance. The influence of baseline $etCO_2$ levels was assessed separately. Statistical analyses were performed with IBM SPSS statistics 21 and R (R Core Team, 2012) with the lme4 package.

Results

Clinical characteristics are shown in Table 1. From the complete cohort of 102 ventilated infants with continuous $etCO_2$ monitoring during the first 72hours after birth who were born between October 2009 and January 2016, we collected a complete dataset in 38 infants born extremely or very preterm. All infants had NIRS monitoring and 33 patients were monitored with amplitude-integrated EEG. A total of 60 episodes of acute $etCO_2$ increases and 70 episodes of acute $etCO_2$ decreases were identified. Corresponding pCO_2 levels were generally within physiologic limits. During $EtCO_2$ increases, $etCO_2$ increased from (mean±SD) 38.0±5.2mmHg to 46.4±5.8 mmHg and then returned to baseline 38.6±5.2mmHg ($p<0.001$). During $etCO_2$ decreases, $etCO_2$ changed from (mean±SD) 40.3±5.8mmHg to 30.4±6.7 mmHg and returned to 39.7±5.2mmHg ($p<0.001$).

Table 1. Clinical characteristics.

	n=38
Gestational age (wk), mean ± SD	29.4 ± 1.8
Birth weight (g), mean ± SD	1358 ± 306
Gender M/F, n (%)	25/13 (66/34)
Antenatal corticosteroids	20 (53)
Apgar 5 min, median [range]	7 [0 – 10]
Hemoglobin on admission (mmol/L), mean±SD	9.9±1.3
Patent ductus arteriosus, n (%)	10 (26)
Respiratory distress syndrome, n (%)	35 (92)
Sepsis, n (%)	4 (11)
Intraventricular haemorrhage, n (%) • No • Mild (grade I/II) • Severe (grade III/IV)	 20 (53) 11 (29) 7 (18)
Deceased, n (%)	3 (8%)

Intraventricular haemorrhages graded by Papile et al.[14]
Moderate-to-severe respiratory distress syndrome: surfactant therapy.

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Table 2. Acute changes in end-tidal CO_2

	$etCO_2$ increase n=60				$etCO_2$ decrease n=70			
	Before	**During**	**After**	**p-value**	**Before**	**During**	**After**	**p-value**
$etCO_2$ (mmHg)	38.0 ± 5.2	46.4 ± 5.8*#	38.6 ± 5.2	*#:<.001	40.3 ± 5.8	30.4 ± 6.7*#	39.7 ± 5.2	*#:<.001
$rScO_2$ (%)	66.0 ± 6.6	71.1 ± 7.8*#	66.8 ± 6.7	*#:<.001	69.6 ± 10.3	61.9 ± 10.1*#	68.4 ± 9.5	*#:<.001
FTOE	0.29 ± 0.07	0.23 ± 0.08*#	0.28 ± 0.08	*#:<.001	0.27 ± 0.11	0.34 ± 0.10*#	0.27 ± 0.10	*#:<.001
SATrate (/min)	5.5 ± 1.6	4.9 ± 1.9#	5.8 ± 1.7	#:<.01	5.3 ± 1.9	5.7 ± 2.0	5.2 ± 2.0	ns
ISI (s)	8.7 ± 4.3	11.2 ± 8.4*#	8.1 ± 4.4	*:<.01 #:<.001	10.1 ± 8.6	9.8 ± 9.1	10.9 ± 11.2	ns
HR (/min)	151 ± 12	151 ± 12#	154 ± 12+	*+:<.01	146 ± 11	152 ± 14*#	145 ± 10	*#:<.001
MABP (mmHg)	36 ± 5	37 ± 5	35 ± 4	ns	35 ± 5	35 ± 5	36 ± 4	ns
SaO_2 (%)	93 ± 4	93 ± 3	93 ± 4	ns	95 ± 3	93 ± 4*	94 ± 2+	*:<.01 +:<.05

Values are depicted as means ± standard deviations. $etCO_2$: end-tidal carbon dioxide; FTOE: fractional tissue oxygen extraction; GA: gestational age; HR: heart rate; ISI: interSATinterval; MABP: mean arterial blood pressure; $rScO_2$: regional cerebral oxygen saturation; SAT: spontaneous activity transient; SaO_2: arterial oxygen saturation. Statistically significant markers: *During vs. Before $etCO_2$ change; # During vs. After $etCO_2$ change; + After vs. Before $etCO_2$ change

To test the validity of the use of $etCO_2$ as a surrogate-marker of pCO_2, a sub-analysis of 10 patients was performed, comparing 128 pairs of pCO_2 and $etCO_2$ values. The mean difference was 7.4 mmHg with a significant correlation (r=0.874, p<0.001).

During acute $etCO_2$ increases, the $rScO_2$ increased and FTOE decreased, and both measures returned to baseline values with $etCO_2$ recovery (Table 2). Linear mixed effects model analysis confirmed these results, with additional predictive effects of SaO_2 for $rScO_2$ (p<0.001) and GA for both $rScO_2$ and FTOE (p<0.05). Similar results were obtained when $etCO_2$ was analysed as a continuous predictor, although GA no longer had a significant effect. There were no interactions between SaO_2, GA and $etCO_2$. Electrical activity decreased slightly during acute $etCO_2$ increase, with a reduction in the SATs rate and increase in ISI length (Table 2). The same results were obtained with linear mixed effect model analysis when $etCO_2$ was included as a categorical or as a continuous predictor, with an additional predictive effect of GA (p<0.001). There was no interaction between $etCO_2$ and GA (Tables 3 and 4; Figure 1).

During acute $etCO_2$ decreases, the $rScO_2$ decreased and FTOE increased, with recovery after $etCO_2$ returned to baseline values (Table 2). Linear mixed effect model analysis confirmed these results, both with $etCO_2$ as a categorical and as a continuous predictor. SaO_2 had a significant additional predictive effect for $rScO_2$. Electrical activity increased slightly but not statistically significant during $etCO_2$ decrease (Table 2). However, a small but significant increase in SATs per min (p<0.05) during a decrease in $etCO_2$ was found with linear mixed effect model analysis, with an additional effect of GA (p<0.05). ISI length was not affected significantly on linear mixed effect model analysis (Tables 3 and 4; Figure 2).

For cerebral oxygenation, inclusion of PDA, postnatal age, vital parameters HR and MABP, or baseline $etCO_2$ did not have a significant effect in any of the models. For electrical activity, inclusion in the models of morphine, postnatal age, vital parameters HR and MABP, or baseline $etCO_2$ did not have an effect (Tables 3, 4).

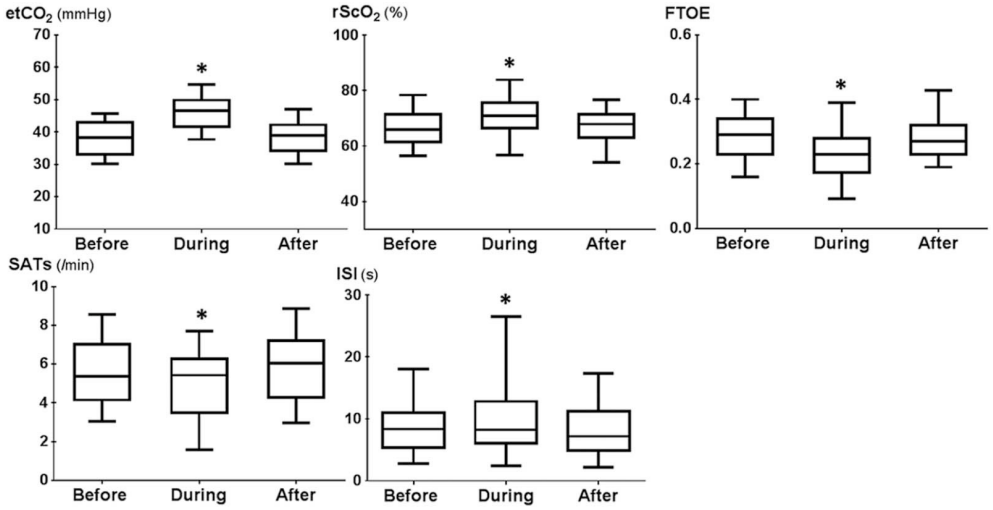

Figure 1. Acute $etCO_2$ increase. $etCO_2$: end-tidal carbon dioxide; FTOE: fractional tissue oxygen extraction; ISI: interSATinterval; $rScO_2$: regional cerebral oxygen saturation; SAT: spontaneous activity transient; *: significant change p<0.05

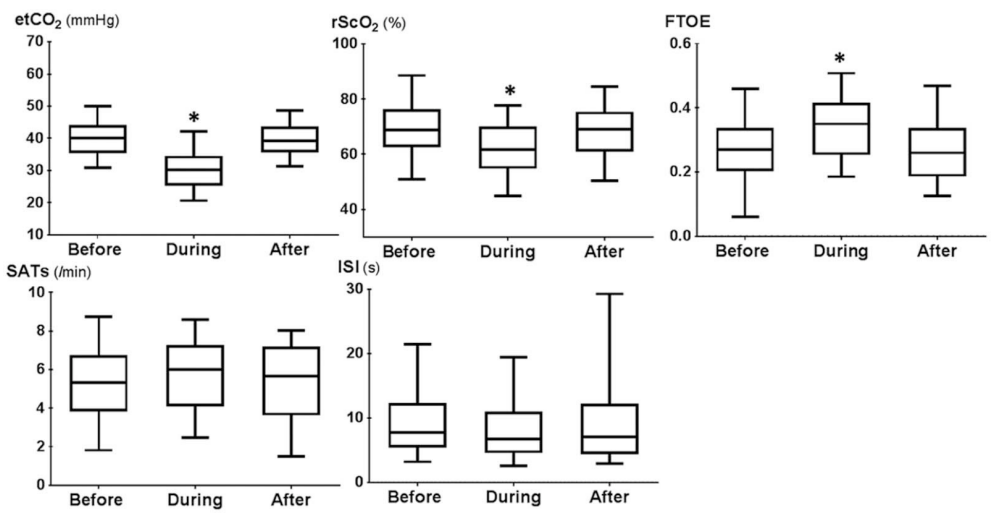

Figure 2. Acute $etCO_2$ decrease. $etCO_2$: end-tidal carbon dioxide; FTOE: fractional tissue oxygen extraction; ISI: interSATinterval; $rScO_2$: regional cerebral oxygen saturation; SAT: spontaneous activity transient; *: significant change p<0.05

Table 3. Linear mixed-effects model analysis with $etCO_2$ as categorical predictor.

	$etCO_2$ increase		$etCO_2$ decrease	
	Coefficient [95% CI]	p- value	Coefficient [95% CI]	p- value
$rScO_2$ (%)				
Constant	-31.54 [-63.34 – 0.26]	.05	4.07 [-21.27 – 29.45]	ns
Period				
• during $etCO_2$ change	4.80 [3.24 – 6.35]	<.001	-6.80 [-8.01 – -5.52]	<.001
• after $etCO_2$ change	0.41 [-1.16 – 4.97]	ns	-0.60 [-1.84 – 0.65]	ns
GA	0.88 [0.17 – 1.58]	<.05		
SaO_2	0.78 [0.53 – 1.04]	<.001	0.69 [0.42 – 0.96]	<.001
FTOE				
Constant	0.56 [0.34 – 0.77]	<.001	0.27 [0.24 – 0.29]	<.001
Period				
• during $etCO_2$ change	-0.05 [-0.07 – -0.04]	<.001	0.07 [0.06 – 0.08]	<.001
• after $etCO_2$ change	0 [-0.02 – 0.011]	ns	0.01 [-0.01 – 0.02]	ns
GA	-0.01 [-0.02 – 0]	<.05		
SATrate (/min)				
Constant	-3.23 [-7.43 – 0.98]	ns	-5.26 [-11.10 – 0.89]	ns
Period				
• during $etCO_2$ change	-0.54 [-1.02 – -0.05]	<.05	0.53 [0.11 – 0.94]	<.05
• after $etCO_2$ change	0.38 [-0.11 – 0.86]	ns	0.04 [-0.38 – 0.46]	ns
GA	0.30 [0.16 – 0.45]	<.001	0.37 [0.15 – 0.59]	<.01
ISI (s)				
Constant	35.59 [20.54 – 50.65]	<.001	53.13 [19.59 – 86.66]	<.001
Period				
• during $etCO_2$ change	2.52 [0.77 – 4.27]	<.01	-0.55 [-2.14 – 1.04]	ns
• after $etCO_2$ change	-0.66 [-2.41 – 1.09]	ns	0.70 [-0.90 – 2.29]	ns
GA	-0.93 [-1.45 – -0.40]	<.001	-1.52 [-2.72 – -0.32	<0.05

CI: confidence interval; $etCO_2$: end-tidal carbon dioxide; FTOE: fractional tissue oxygen extraction; GA: gestational age; ISI: interSATinterval; $rScO_2$: regional cerebral oxygen saturation; SaO_2: arterial oxygen saturation; SAT: spontaneous activity transient.

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Table 4. Linear mixed-effects model analysis with $etCO_2$ as continuous predictor.

	$etCO_2$ increase		$etCO_2$ decrease	
	Coefficient [95% CI]	**p- value**	**Coefficient [95% CI]**	**p- value**
$rScO_2$ (%)				
Constant	-20.71 [-45.00 – 3.58]	ns	-20.69 [-44.70 – 3.32]	ns
$EtCO_2$	0.46 [0.33 – 0.60]	<.001	0.59 [0.49 – 0.68]	<.001
SaO_2	0.75 [0.50 – 1.01]	<.001	0.70 [0.44 – 0.96]	<.001
FTOE				
Constant	0.48 [0.42 – 0.54]	<.001	0.52 [0.48 – 0.57]	<.001
$EtCO_2$	-0.01 [-0.01 – 0]	<.001	-0.01 [-0.01 – -0.01	<.001
SATrate (/min)				
Constant	-1.89 [-6.24 – 2.46]	ns	-3.55 [-9.56 – 2.46]	ns
$EtCO_2$	-0.06 [-0.10 – -0.03]	.001	-0.05 [-0.08 – -0.02]	.001
GA	0.34 [0.19 – 0.50]	<.001	0.38 [0.17 – 0.59]	<.001
ISI (s)				
Constant	30.44 [14.55 – 46.33]	<.001	50.94 [17.18 – 84.70]	<.01
$EtCO_2$	0.27 [0.13 – 0.41]	<.001	0.07 [-0.05 – 0.19]	ns
GA	-1.11 [-1.66 – -0.56]	<.001	-1.54 [-2.73 – -0.34]	<.05

CI: confidence interval; $etCO_2$: end-tidal carbon dioxide; FTOE: fractional tissue oxygen extraction; GA: gestational age; ISI: interSATinterval; $rScO_2$: regional cerebral oxygen saturation; SaO_2: arterial oxygen saturation; SAT: spontaneous activity transient.

Discussion

Our study shows that an acute increase in CO_2 is associated with an increase in cerebral oxygenation and decrease in electrical activity. Conversely, an acute decrease in CO_2 reduces cerebral oxygenation, with a small increase in cerebral activity.

The $etCO_2$ was used as a surrogate marker for pCO_2. Arterial pCO_2 is the gold standard in neonatal intensive care to assess ventilation efficiency. The $etCO_2$ can be monitored continuously in ventilated infants without the disadvantages of arterial sampling such as blood loss, the necessity for top-up transfusions, or catheter-related complications. The correlation between pCO_2 and $etCO_2$ is well defined, where $etCO_2$ values are on average slightly lower. Rozycki et al found a highly significant correlation between $etCO_2$ and pCO_2 ($r=0.833$, $p<0.001$).[11] The mean $etCO_2$ was 6.9 mmHg lower compared to mean pCO_2, and the difference between 2 consecutive pCO_2 values was similar to that between 2 consecutive $etCO_2$ values. Wu et al found a similar correlation ($r=0.849$, $p<0.001$) but a smaller difference of 3.5 mmHg between $etCO_2$ and pCO_2.[12] We confirmed this correlation in our own study population. However, $etCO_2$ monitoring may not be suitable for all patients. In extremely low birth weight infants, the $etCO_2$ cannot be monitored accurately because of low sample volume issues owing to low tidal volumes.[19] Transcutaneous CO_2 monitoring might be an alternative for $etCO_2$ monitoring, however this modality was beyond the scope of this study. Future studies should confirm if, in the absence of $etCO_2$ monitoring, continuous NIRS monitoring could be used as an early warning system.

Our study shows that fluctuations in CO_2 affect cerebral oxygenation (and perfusion), which is in line with previous research.[20,21] The study by Wyatt et al included 17 infants, both preterm and at term. The question whether infants born preterm respond differently to acute changes in CO_2 than infants born at term remains unanswered. It has been suggested that cerebral blood flow reactivity to CO_2 might be diminished in mechanically ventilated preterm infants on the first day after birth.[22] In addition, autoregulation may affect cerebral oxygenation during the first days after birth, but our patient population was too small to take this into account.[6,23] Autoregulation remains an important issue for future research.

In our study, an acute increase in pCO_2 diminished brain activity with a decreased SATs rate and increased ISI length.[18] Other studies have also demonstrated the association between an increase in pCO_2 and a reduction in cerebral electrical activity, with lengthening of the interburst interval (comparable to ISI) on the EEG of infants born preterm.[24,25] Brain activity during the first postnatal days is related to brain growth, both total brain volume and subcortical gray matter, and important for survival of neurons and cerebral network development.[26,27] Reduced cerebral electrical activity, longer duration of IBI, in infants born preterm has been associated with adverse neurological outcome.[28] Therefore, reduced brain activity caused by sudden increases in CO_2 may have a negative effect on brain development.

It remains unclear if the cerebral effects are caused directly by CO_2, or by CO_2-induced changes in perivascular pH or bicarbonate. CO_2 can easily diffuse across the blood-brain barrier and induce changes in interstitial pH of the brain.[29] Hypercapnia increases the H+ concentration, resulting in relaxation of cerebral vascular smooth muscle cells. Acute changes in pCO_2 have a different effect on the brain than chronic abnormal pCO_2 levels. In newborn piglets, an increase in CO_2 resulted in increased cerebral blood flow, but after 4 hours of chronic hypercapnia cerebral flow had returned to baseline levels. During chronic CO_2 abnormalities, pH will eventually normalize by buffer capacity with restoration of cerebral blood flow.

For this study, we only selected infants on mechanical ventilation and $etCO_2$ monitoring

who showed acute $etCO_2$ fluctuations of at least 5mmHg within the first 72h after birth. Our stringent inclusion criteria resulted in a small, heterogeneous study population of sick infants born preterm. As shown in Table 1, the incidence of IVH was relatively high in this cohort (mild IVH grade I/II according to Papile: 29% and severe IVH grade III/IV according to Papile: 18%), compared to an overall incidence of IVH of approximately 20% in the general preterm population.[14,30] Also, cerebral autoregulation may be impaired in sick infants, which may have increased their response to CO_2 fluctuations.[31] Although beyond the scope of this study, 'physiological' pCO_2 fluctuations that do not reach extreme seem to affect the neonatal brain and might contribute to cerebral complications. NIRS monitoring could be considered as a candidate to evaluate these effects of CO_2. For the present study, it was decided a priori that a change of at least 5 mmHg in $etCO_2$ would qualify as a significant fluctuation. Although this is an arbitrary limit, the study results show that these fluctuations affect cerebral oxygenation and electrical activity. These variables also reflect cerebral perfusion and might, therefore, be damaging to the neonatal brain. Fluctuations in cerebral perfusion are associated with severe IVH (grade III/IV) and adverse neurodevelopmental outcome at 18 to 22 months of age.[7] Reducing fluctuations in cerebral oxygenation and perfusion might improve neurodevelopmental outcomes.

Several limitations should be mentioned. This study has an observational retrospective design, without induced $etCO_2$ variations or selective patient inclusion, comprising a small sample. Although we did correct for variables that may influence cerebral oxygenation and activity, such as postnatal age, HR and MABP, PDA, and morphine, we did not correct for sleep state and position. Sleep state data were not collected continuously and could not be matched to the oxygenation and activity data. Also, the small size and the heterogeneity in obstetric history and early neonatal characteristics of our patient group may prohibit application of our findings to a more general population of infants born very preterm. The NIRS small adult sensor was used for cerebral oxygenation monitoring. New, smaller sensors are now available, suitable for the smallest neonates. Our research group has previously shown that these neonatal sensors measure an average 10% higher compared to the adult sensors, losing variability in the higher regions.[16] We therefore used the small adult sensor. Finally, we were unable to determine autoregulation, which is also known to influence cerebral vascular CO_2 reactivity. Nevertheless, the consistency of our findings makes them significant and well worth pursuing in further studies.

The clinical importance of this study is that hypocapnia and hypercapnia, as well as CO_2 fluctuations, have been associated with neurologic pathology.[32,33] In a study in newborn piglets, the brain received a significantly higher proportion of cardiac output after a mild increase in CO_2, although the total cardiac output remained unchanged.[5] A recent study by Chandrasekharan et al., used an animal model of asphyxiated term lambs with meconium aspiration to compare the addition of $etCO_2$-monitoring to a control group with only pCO_2 arterial gas analysis.[34] They demonstrated that pCO_2 and $etCO_2$ were correlated significantly, and that fluctuations in pCO_2 and cerebral blood flow were significantly less in the group with $etCO_2$-monitoring. The authors suggest that continuous monitoring of CO_2 is important to prevent fluctuations in pCO_2, which is in line with our study. NIRS monitoring could be considered as an alternative when $etCO_2$ monitoring is not available.

Conclusion

Fluctuations in pCO_2, even within the normal range, seem to affect neonatal cerebral oxygenation and electrical activity directly. Clinicians should be aware of these effects and consider continuous CO_2 monitoring in combination with NIRS and EEG to identify and limit the effects of CO_2 fluctuations, to improve cerebral stability. Future research should confirm these results in a large prospective study, and also address the potential implications for preventing neurological injury and improving long-term outcomes.

9

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9

Severe hypercapnia causes reversible depression of aEEG background activity in neonates: an observational study

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Lauren C. Weeke[1], Laura M. L. Dix[1]
Floris Groenendaal[1], Petra M. A. Lemmers[1]
Koen P. Dijkman[2], Peter Andriessen[2,3]
Linda S. de Vries[1], Mona C. Toet[1]

[1] Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands.
[2] Department of Neonatology, Máxima Medical Center, Veldhoven, The Netherlands.
[3] Department of Pediatrics, Faculty of Health, Medicine and Life Science, University of Maastricht, Maastricht, The Netherlands

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CHAPTER 10

Severe hypercapnia causes reversible depression of aEEG background activity in neonates: an observational study

Abstract

Background Elevated carbon dioxide (CO_2) blood levels have a depressant effect on the central nervous system and can lead to coma in adults. Less is known about the effect of CO_2 on the neurological function of infants.

Objective To describe the effect of acute severe hypercapnia ($PaCO_2$ >70 mm Hg) on amplitude-integrated electroencephalography (aEEG) and cerebral oxygenation in newborn infants.

Methods Observational study of full-term and preterm infants with acute severe hypercapnia (identified by arterial blood gas measurements), monitored with aEEG. Visual analysis of the aEEG was performed in all infants. In preterm infants <32 weeks postmenstrual age (PMA), analysis of two-channel EEG was performed. Mean spontaneous activity transients (SAT) rate (SATs/min), interval between SATs (ISI in seconds) and the ISI percentage (ISP) were calculated for 10-min periods before, during and after hypercapnia. Mean regional cerebral oxygen saturation ($rScO_2$) and fractional tissue oxygen extraction (FTOE) measured with near-infrared spectroscopy were also calculated for these periods.

Results Twenty-five infants (21 preterm, 4 full-term) comprising 32 episodes of acute severe hypercapnia were identified. Twenty-seven episodes were accompanied by a transient aEEG depression. Twenty-two episodes in 15 preterm infants <32 weeks PMA were quantitatively analysed. During hypercapnia, SAT rate decreased and ISI and ISP increased significantly. No significant change occurred in $rScO_2$ or FTOE during hypercapnia.

Conclusion Profound depression of brain activity due to severe hypercapnia is also seen in infants. It can be recognised by an acute depression of the aEEG, without clinically detectable changes in cerebral oxygenation.

Introduction

Elevated carbon dioxide (CO_2) blood levels have a depressant effect on the central nervous system and electroencephalography (EEG) activity.[1,2] In adults, hypercapnia can lead to an altered mental state, encephalopathy and coma.[3] CO_2 narcosis has been described in adults with a $PaCO_2$ of 62-269 mm Hg, but the cerebral response to hypercapnia showed a broad inter-individual variability.[2] Less is known about the effect of high CO_2 on the neurological function in infants. High CO_2 levels usually occur in critically ill infants, in whom neurological examination can be difficult, especially when they are preterm and/or sedated. However, EEG and amplitude-integrated EEG (aEEG) are now widely used in the neonatal intensive care unit (NICU) to monitor brain activity. In preterm infants, the depressant effect of CO_2 on EEG has been described. Hypercapnia resulted in longer interburst intervals (IBIs) and decreased total EEG power.[4,5] The phenomenon of CO_2 narcosis as seen in adults has not been described in infants. The aim of this study was to describe the effect of acute, severe hypercapnia on brain activity, cerebral oxygenation and haemodynamics in infants. Our hypothesis was that CO_2-mediated neurological suppression also occurs in the neonatal period and results in profound EEG depression, an increase in cerebral oxygenation due to vasodilatation and a decrease in cerebral oxygen consumption due to reduced brain activity, without significant changes in haemodynamic parameters.

Methods

Patients

This was an observational study in two Dutch level III NICUs followed by retrospective data analysis. Full-term and preterm infants with acute severe hypercapnia ($PaCO_2$ >70 mm Hg) while being monitored with aEEG between April 2009 and May 2015 were included. To report anonymous data of clinical events, a waiver to obtain ethical approval for the study was received from the ethical committee of both hospitals in compliance with Dutch national regulations.

Neuromonitoring (aEEG and near-infrared spectroscopy)

Continuous neuromonitoring included aEEG, to assess brain activity and screen for seizures, and near-infrared spectroscopy (NIRS), to assess cerebral oxygenation. Neuromonitoring was performed as standard of care in the Wilhelmina Children's Hospital in Utrecht, in infants following preterm birth <28 weeks of gestation, when at risk for developing seizures (e.g. sepsis, meningitis, perinatal asphyxia), during surgery and during therapeutic hypothermia in both centres. For single-channel aEEG (P4-P3), the Olympic 6000 cerebral function monitor (Natus, Seattle, Washington, USA) was used. For two-channel aEEG (F4-P4, F3-P3) digital BRM_2 and BRM3 BrainZ (Natus) and NicoletOne (Natus) monitors were used. To assess regional cerebral oxygen saturation ($rScO_2$) and fractional tissue oxygen extraction (FTOE), a two-wavelength (730 and 810 nm) near-infrared spectrometer (INVOS 4100-5100, Covidien, Mansfield, Massachusetts, USA) with a fronto-parietal transducer (small adult SomaSensor SAFB-SM, Covidien) was used.

Haemodynamic parameters

Heart rate, mean arterial blood pressure (MABP), measured via an indwelling arterial catheter, and arterial oxygen saturation (SaO_2) were monitored in all infants using a Philips Intellivue MP70 patient monitor. The fraction of inspired oxygen (FiO_2) as measured on the ventilator was documented every minute.

Blood gas analysis

Arterial blood gas measurements (including pH, $PaCO_2$, PaO_2, base excess, bicarbonate and glucose) were performed intermittently, mostly with a four hourly interval, depending on the infant's clinical condition.

Data analysis

The aEEG background activity was visually determined in all infants, both full-term and preterm, by an experienced neonatologist (MCT), who was blinded to the $PaCO_2$ levels, using the background activity classification described by Toet et al.[6] The raw EEG signal of infants monitored with a BRM BrainZ monitor and, simultaneous $rScO_2$, FTOE, heart rate, MABP and SaO_2 measurements were analysed using in-house developed software (SignalBase, version 8.5.2, University Medical Center Utrecht, Utrecht, the Netherlands). Artefacts caused by, for example, movement in any of the signals were manually removed. Only infants with a postmenstrual age (PMA) <32 weeks at the time of hypercapnia were included because the quantitative analysis of the raw EEG signal can only be reliably performed on discontinuous EEG backgrounds. After 32 weeks PMA, the EEG becomes more continuous. The raw EEG signal (P4-P3, sample rate 256 Hz) was segmented into spontaneous activity transients (SATs, periods of cortical activity) and interSAT intervals (ISIs, time between SATs, periods of cortical inactivity, comparable to IBI) using a non-linear energy operator in the SignalBase software.[7] This method assumes that the EEG consists of periods of activity alternated with periods of inactivity, which corresponds to

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a discontinuous background activity. For each infant, a 10-min period was selected 5-10 min before a documented $PaCO_2$ >70 mm Hg. Another 10-min period was selected 5-10 min before the first documented $PaCO_2$ in the normal range (35-45 mm Hg) before and after hypercapnia. In case of permissive hypercapnia, which is the acceptance of hypercapnia in infants in whom ventilation is difficult, the first documented $PaCO_2$ <60 mm Hg before and after hypercapnia was chosen. For each period (before, during and after), the mean number of SATs per minute (SATrate), mean ISI duration in seconds and the percentage of the recording made up by ISI (ISP) were calculated. Mean values of $rScO_2$, FTOE, heart rate, MABP, SaO_2 and FiO_2 were calculated for each period as well.

Statistical analysis

SPSS version 21 (IBM, Armonk, New York, USA) was used to perform t-test or Fisher's exact test to compare the patient characteristics between infants with and without a visual aEEG change. Repeated measures analysis of variance (ANOVA) with Bonferroni correction or Friedman's ANOVA in case of non-normally distributed data was performed to compare periods before, during and after hypercapnia. A p-value <0.05 was considered statistically significant.

Results

Twenty-five infants with a total of 32 episodes (two episodes n = 1, three episodes n = 3) of acute, severe hypercapnia were identified. Four were full-term infants (≥37 weeks gestational age [GA]) and 21 were preterm. Hypercapnia was caused by suboptimal mechanical ventilation (n = 15, 46.9%), tube obstruction (n = 9, 28.1%), pneumothorax (n = 4, 12.5%), tube dislocation (n = 1, 3.1%), pulmonary haemorrhage (n = 1, 3.1%), pulmonary interstitial emphysema (n = 1, 3.1%) or respiratory insufficiency (n = 1, 3.1%). The reasons for EEG monitoring were postoperative monitoring (n = 13, 40.6%), preterm birth <28 weeks gestation (n = 9, 28.1%), being at risk of developing seizures (n = 7, 21.9%) and therapeutic hypothermia (n = 3, 9.4%). Only one infant was not on the ventilator at the time of hypercapnia, this was a preterm born infant, who presented at a PMA of 35.5 weeks with acute, severe hypercapnia five hours after extubation, due to respiratory insufficiency, but without a visible change in the aEEG. Patient characteristics are shown in Table 1.

Visual analysis aEEG — full-term and preterm infants

Twenty-seven episodes of severe hypercapnia were accompanied by a sudden depression of the aEEG trace (Figure 1), from discontinuous normal voltage (DNV) to dense burst suppression (BS+) in six (18.8%), to sparse burst suppression (BS–) in six (18.8%) and to flat trace (FT) in four (12.5%), from BS+ to BS- in six (18.8%) and to FT in one (3.1%), from BS- to FT in two (6.3%), from continuous normal voltage to DNV in one (3.1%) and to FT in one (3.1%). The background activity recovered within one hour of normalisation of the $PaCO_2$ in all patients. During five hypercapnic episodes no change in the aEEG trace was seen. No significant difference in $PaCO_2$ or other clinical parameters was found between those with and those without a visible change in the aEEG trace (Table 1). However, infants without a visible aEEG change tended to have a higher GA at birth and were older at the time of hypercapnia (p = 0.081).

Quantitative analysis — preterm infants

Data from 15 preterm infants <32 weeks PMA comprising 22 hypercapnic episodes were available for quantitative data analysis. Mean blood gas measurements and EEG, cerebral oxygenation and haemodynamic parameters before, during and after hypercapnia are shown in Table 2. Electroencephalography: a significant decrease in SATrate and increase in ISI and ISP was seen during hypercapnia (Table 2, Figure 2A, E). Of the three episodes not accompanied by a visual depression in the aEEG, two showed a decrease in SATrate and increase in ISI and ISP during hypercapnia, one showed an increase in SATrate and decrease in ISI and ISP during hypercapnia. Cerebral oxygenation: a non-significant increase in $rScO_2$ and decrease in FTOE were seen during hypercapnia (Table 2, Figure 2B, F). Haemodynamic parameters: no changes in heart rate and MABP were seen during hypercapnia (Table 2, Figure 2C, G). SaO_2 decreased non-significantly during hypercapnia but increased significantly afterwards. FiO_2 increased significantly during hypercapnia (Table 2, Figure 2D, H).

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Table 1. Patient characteristics.

Total n=25 patients n=32 episodes	Preterm n=21	Full-term n=4	Visible aEEG change n=27	No visible aEEG change n=5	p-value
Male, n (%)	12 (57.1)	1 (25)	14 (51.9)	3 (60)	1.000
GA at birth (weeks)	27.3 (25.0-29.5)	38.5 (38.2-40.6)	27.3 (25.1-32.1)	29.2 (25.6-32.6)	0.920
Birth weight (grams)	935 (750-1468)	3218 (2729-3845)	935 (750-1490)	1150 (890-1905)	0.968
GA at hypercapnia (weeks)	28.6 (26.5-31.2)	39.1 (38.5-41.0)	28.4 (26.3-32.3)	30.0 (27.4-37.3)	0.479
Age at hypercapnia (hours)	120 (46.5-441.4)	20.7 (7.2-131)	89.4 (39.0-309.2)	454.4 (112.7-934.5)	0.081
Sedatives, n (%)	18 (85.7)	4 (100)	25 (92.6)	4 (80)	0.410
Duration sedatives before aEEG change (hours)	27.3 (13.9-44.5)	16.6 (4.1-112)	23.4 (14.3-54.8)	61.1 (6.7-477.1)	0.831
IVH, n (%)					0.499
• no	4 (19)	4 (100)	9 (34.6)	1 (20)	
• IVH before hypercapnia, no progression	8 (38.1)	0	10 (38.5)	3 (60)	
• IVH before hypercapnia, progression	3 (14.3)	0	2 (7.7)	1 (20)	
• IVH after hypercapnia	5 (23.8)	0	5 (19.2)	0	

Results in median (IQR) unless otherwise specified.
aEEG: amplitude-integrated EEG; GA: gestational age; IQR: interquartile range; IVH: intraventricular haemorrhage.

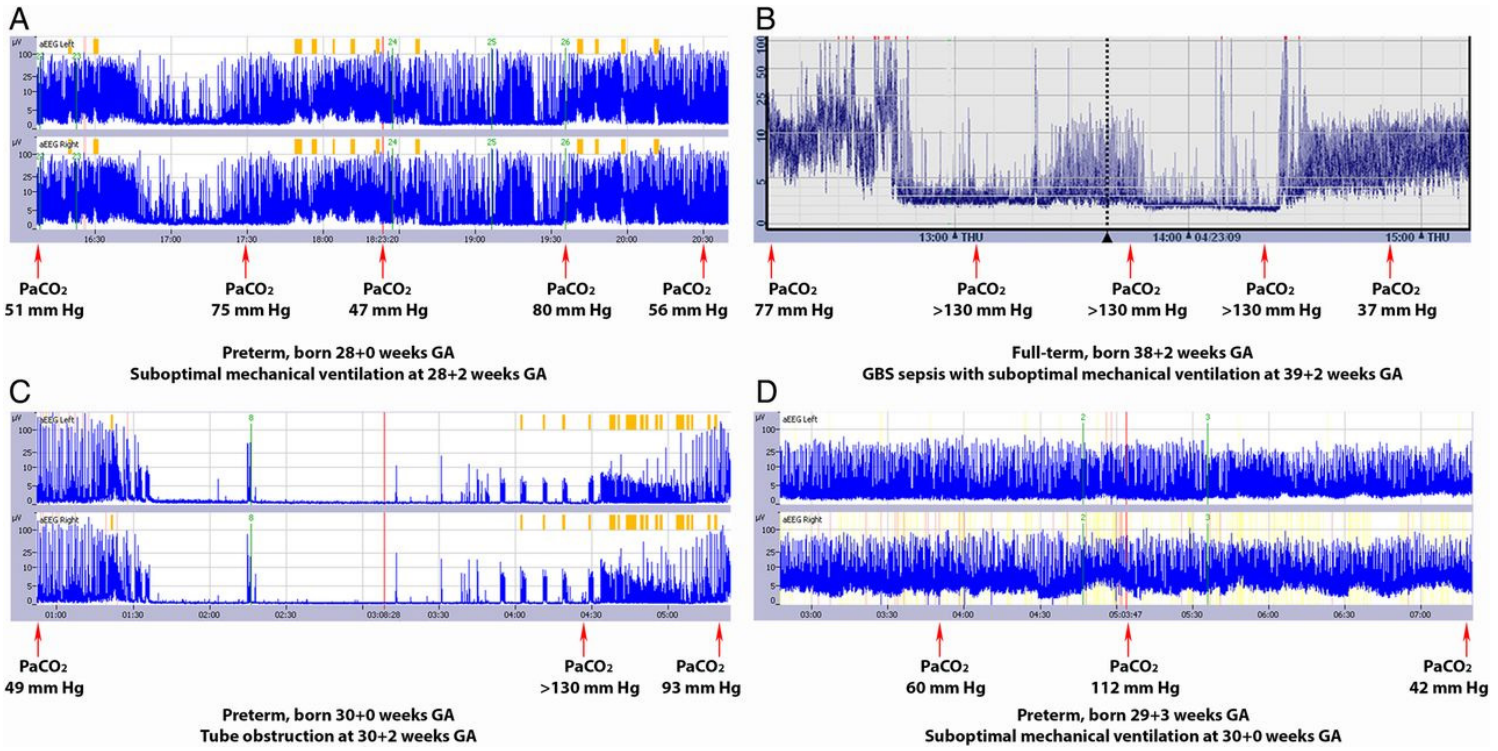

Figure 1. Examples of amplitude-integrated electroencephalography (aEEG) traces showing a sudden, but transient depression during hypercapnia (A-C). In panel D, no change in the aEEG trace was observed during hypercapnia. GA: gestational age; GBS: Group B Streptococcus.

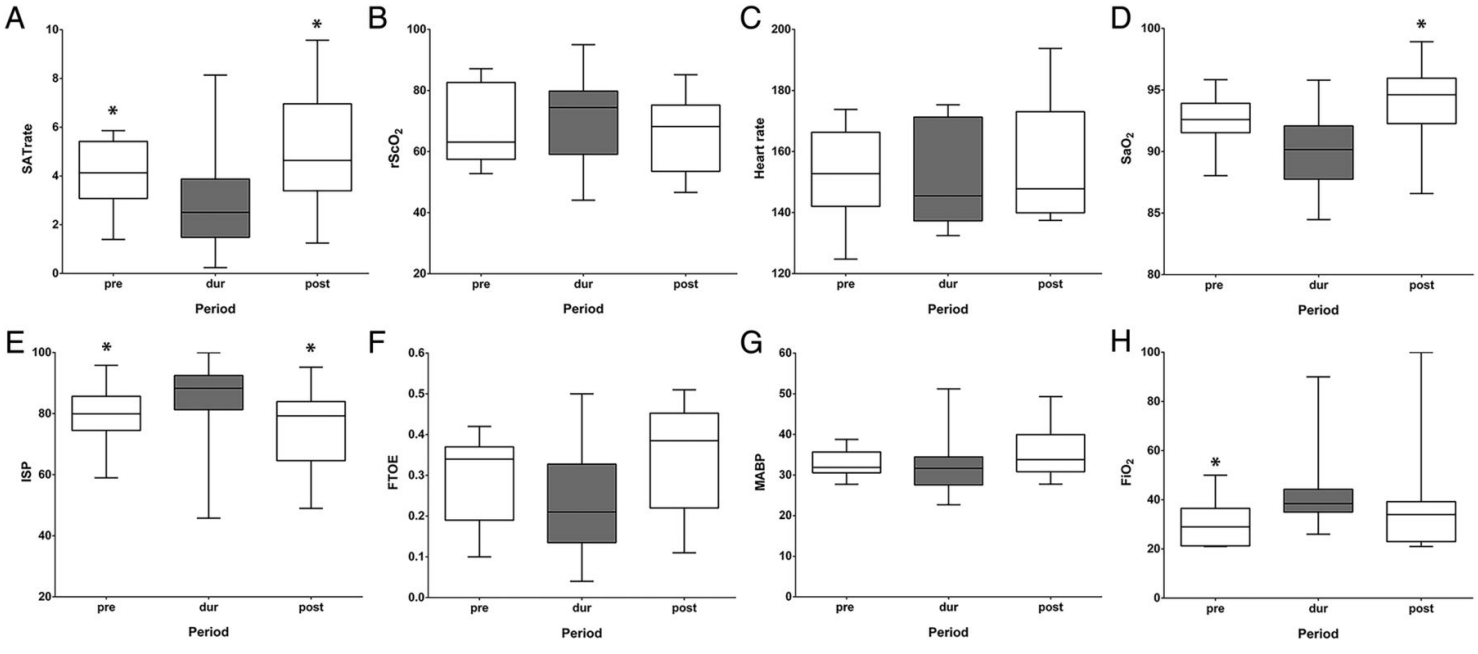

Figure 2. Boxplots comparing mean values of A) SATrate: spontaneous activity transients/minute, B) $rScO_2$: regional cerebral oxygen saturation, C) heart rate, D) SaO_2 arterial oxygen saturation, E) ISP: interSAT percentage, F) FTOE: fractional tissue oxygen extraction, G) MABP: mean arterial blood pressure, H) FiO_2: fraction inspired oxygen, before (pre), during (dur) and after (post) hypercapnia. *: significant change compared with the period during hypercapnia.

Table 2. Blood gas measurements and EEG, cerebral oxygenation and haemodynamic parameters before, during and after hypercapnia in the 22 hypercapnic events that were quantitatively analysed.

Blood gas measurements	Before, median time 3:06 (hour:min) IQR 2:05-4:03	During	After, median time 1:25 (hour:min) IQR 0:55-2:46	p-value
pH	7.26 (0.04)	7.02 (0.10)	7.27 (0.04)	<0.001*,†
$PaCO_2$ (mm Hg)	50.70 (5.96)	95.65 (16.45)	49.40 (6.50)	<0.001*,†
PaO_2 (mm Hg)	57.05 (12.74)	57.70 (13.34)	60.15 (31.58)	0.892
Base excess (mmol/l)	-4.39 (1.72)	-5.39 (2.62)	-4.22 (1.99)	0.295*, 1.000†
Bicarbonate (mmol/l)	22.64 (1.66)	25.14 (2.15)	22.61 (1.98)	<0.001*,†
Glucose (mmol/l)	6.64 (1.82)	7.82 (1.79)	6.96 (1.56)	0.086

Quantitative parameters	Before	During	After	p-value
EEG				
• SATrate (/min)	4.06 (1.28)	2.42 (1.47)	4.88 (2.34)	<0.001*,†
• ISI (sec)	13.00 (5.64)	33.10 (36.17)	12.59 (9.57)	0.004*, <0.001†
• ISP (%)	79.24 (9.12)	87.91 (6.84)	76.12 (13.50)	0.001*, <0.001†
Cerebral oxygenation				
• $rScO_2$ (%)	66.54 (12.01)	68.36 (11.66)	65.91 (13.22)	1.000
• FTOE	0.32 (0.09)	0.23 (0.14)	0.35 (0.14)	0.327*, 0.064†
Haemodynamic parameters				
• Heart rate (/min)	153 (16)	153 (17)	157 (20)	0.895
• Blood pressure (mm Hg)	33.03 (3.44)	32.98 (8.16)	35.11 (6.07)	0.584
• SaO_2 (%)	92.24 (2.11)	89.74 (3.65)	94.29 (2.25)	0.150*, 0.003†
• FiO_2 (%)	30.86 (9.26)	44.30 (15.41)	35.19 (18.76)	0.004*, 0.061†

Results in mean (SD). P-value markers: * before vs. during $PaCO_2$ change; † during vs. after $PaCO_2$ change. FTOE: fractional tissue oxygen extraction; ISI: interSAT interval; ISP: interSAT percentage; IQR: interquartile range; SaO_2: arterial oxygen saturation; SATrate: number of spontaneous activity transients per minute; SD: standard deviation.

Discussion

This study shows that profound depression of brain activity during severe hypercapnia as has been described in adults also occurs in infants. It can be detected by visual inspection of the aEEG trace, showing an acute depression of the background activity, and by quantitative analysis of the EEG, showing a decrease in cortical activity (SATrate) and an increase in cortical inactivity (ISI, ISP). In our cohort, the depression of brain activity was transient. When $PaCO_2$ normalised after hypercapnia, the SATrate, ISI and ISP returned to normal as well. No significant changes were seen in $rScO_2$, FTOE, heart rate and MABP. SaO_2 did not change significantly during hypercapnia, but increased significantly afterwards. Mean values remained within normal ranges mediated through a significant change in FiO_2 from normocapnia to hypercapnia. As seen in adults,[2,8] a broad interindividual variability in response to hypercapnia was seen in our cohort. Some infants showed severe visible aEEG depression and changes inquantitative EEG parameters, while others showed no visible depression to similar levels of hypercapnia and no or an inverse change in quantitative EEG parameters.

The depressant effect of $PaCO_2$ on EEG has been described in preterm infants.[4,5] These studies showed that the IBI increased and the total EEG power decreased with increasing $PaCO_2$. However, the $PaCO_2$ levels in these studies were mainly within the normal range with only a few reaching severe hypercapnia levels. Our results support the findings in these studies and show in addition that $PaCO_2$ also affects the brain activity of full-term infants and that severe hypercapnia results in profound depression of brain activity, which can be clearly visible on the aEEG.

The effect of hypercapnia on cerebral oxygenation parameters such as $rScO_2$ and FTOE has been described by a number of studies.[5,9,10] Hino et al described an increase in cerebral blood flow and oxygen transport in newborn lambs with increasing $PaCO_2$ levels, but saw no increase in oxygen consumption by the brain, leading to an increase in $rScO_2$.[10] A negative linear association between $PaCO_2$ and FTOE has been described, with $PaCO_2$ ranging from hypocapnic to mild hypercapnic levels.[5,9] This association can be explained by the reduction of electrical activity in the brain during hypercapnia, leading to decreased oxygen consumption by the brain, since electrical activity is the most energy requiring process in the brain.[11] These observations are supported by our findings as $rScO_2$ increased during hypercapnia and FTOE decreased. However, we did not find these relations to be significant, unlike Vanderhaegen et al, who described a significant positive linear relation between $PaCO_2$ and the tissue oxygenation index, equivalent to $rScO_2$, in a group of low birth weight preterm infants.[9] This could be explained by the effect of hypoxia on the $rScO_2$. In most of our infants, the SaO_2 decreased during hypercapnia because of an acute respiratory problem. When hypoxia is present, the $rScO_2$ decreases, especially when autoregulation is absent. Therefore, in the presence of hypoxia, the effect of $PaCO_2$ on $rScO_2$ will be attenuated. FTOE corrects for the effect of SaO_2, but was also not significantly affected by the change in $PaCO_2$ from normocapnia to hypercapnia. However, this could be due to the limited number of infants with FTOE values available for analysis.

Many studies have tried to unravel the mechanism of action of CO_2 narcosis. Based on animal and human studies, the most likely hypothesis is that the effect of $PaCO_2$ on the central nervous system is mediated through alteration of the intracerebral pH.[12] Both respiratory and metabolic acidosis have been related to EEG depression, but the depression of cerebral function was more consistently correlated with $PaCO_2$ than bicarbonate levels.[13-15] Furthermore, Victor et al did not find a relation between pH and EEG activity.[5] CO_2 seems to have a more profound effect on brain function, because the blood-brain barrier is permeable to CO_2 and relatively impermeable to bicarbonate ions, causing a more rapid crossing of CO_2 over the blood-brain barrier than hydrogen ions.[16]

Hypoxia has only been related to electrocortical depression at extremely low SaO_2 levels (<24%) in newborn piglets,[17] while a study in newborn lambs showed no effect of hypoxia on electrocortical activity.[18] In our cohort, all SaO_2 values remained within the normal range during hypercapnia. It is therefore unlikely that hypoxia played a role in the observed EEG depression.

Wikström et al showed that plasma glucose levels were also associated with EEG activity.[4] In our cohort, plasma glucose concentration did not change significantly during hypercapnia. It is well known that medication such as morphine and benzodiazepines, which are often used in infants admitted to the NICU for sedation or as antiepileptic drugs, can suppress the EEG.[19,20] The use of sedatives was unlikely to have caused the sudden depression in the aEEG in our cohort because almost all infants were already receiving sedatives for several hours or even days. The fast recovery of the aEEG after normalisation of $PaCO_2$ underlines the profound effect CO_2 has on brain activity, since many of the potential confounding factors, such as the use of sedatives, were constant over this short period of time. It is of interest that during five hypercapnic episodes no EEG depression was visible and that these infants had a higher GA at birth and postnatal age at the time of hypercapnia.

The consequences of CO_2 narcosis in infants are not well known. Extreme fluctuations in $PaCO_2$ and a higher maximum $PaCO_2$ have been associated with worse neurodevelopmental outcome in very low birth weight preterm infants.[21] This may be mediated

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through the induction of brain damage such as intracranial haemorrhage and periventricular leukomalacia.(22, 23) Prolonged depression of cortical function has been associated with impaired outcome in preterm infants.[24,25] However, the EEG depression in CO_2 narcosis is reversible and should therefore be corrected as soon as possible.

This study has some limitations. First, the study design did not allow more thorough investigation of the relation between $PaCO_2$, EEG and cerebral oxygenation, because it was an observational retrospective cohort, without continuous CO_2 measurements. However, in preterm infants reliable end-tidal CO_2 measurements are difficult to obtain. Even though we have no continuous CO_2 data, it is almost certain that hypercapnia was acute in the cases described because $PaCO_2$ was normal during the previous blood gas measurement and the aEEG depression was very sudden. Also, Victor et al showed that chronic hypercapnia does not cause changes in IBI in preterm infants.[26] Second, a comprehensive method for quantitative assessment of EEG in full-term infants is not yet available, limiting quantitative analyses to preterm infants only and reducing the sample size.

Conclusion

In conclusion, acute hypercapnia can cause reversible depression of the aEEG background activity, without clinically detectable changes in cerebral oxygenation and other haemodynamic parameters in infants. A sudden depression in the aEEG background activity in these infants should alert clinicians to suspect a high $PaCO_2$ due to a respiratory problem.

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PART 4

CAFFEINE

Effects of caffeine on the preterm brain: an observational study

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Laura M. L. Dix, Frank van Bel
Willem Baerts, Petra M. A. Lemmers

Department of Neonatology, Wilhelmina Children's Hospital
University Medical Center Utrecht, Utrecht, The Netherlands

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CHAPTER 11

Effects of caffeine on the preterm brain: an observational study

Abstract

Background and objective This study analyses the effects of caffeine on neonatal brain. As caffeine might have a neuroprotective effect, we hypothesize an increase in oxygen metabolism, electrical function and perfusion.

Methods Preterm infants <32 weeks gestation (GA) receiving their primary dose caffeine-base (10mg/kg) were included. Ten minutes of stable monitoring were selected before, during, and every hour up to 6 hours after caffeine. Near-infrared spectroscopy monitored regional cerebral oxygenation ($rScO_2$) and extraction (FTOE). Amplitude-integrated electroencephalogram (aEEG) monitored minimum, mean and maximum amplitudes. Spontaneous activity transients (SAT) rate and the interval between SATs (interSAT interval, ISI) were calculated. Mean arterial blood pressure (MABP), heart rate (HR) and arterial oxygen saturation (SaO_2) were monitored simultaneously. pCO_2's were collected before and 4h after caffeine. Brain perfusion was assessed 1h before and 3h after caffeine by Doppler-measured resistance-index (RI), peak systolic velocity (PSV) and end-diastolic velocity (EDV), in the anterior cerebral artery (ACA) and internal carotid artery (ICA). Results in mean(SD).

Results 34 infants with GA 28.8(2.1) wk. $rScO_2$ (%) decreased significantly from baseline: 69(11), to a nadir 1h after caffeine: 63(12), and recovered at 6h: 66(10). FTOE increased significantly from 0.25(0.12 to a peak 1h after caffeine: 0.32(0.13) and recovered at 6h: 0.28(0.11). MABP and HR increased significantly. PSV in the ACA decreased slightly. Other Doppler variables, aEEG parameters and SaO_2 were unaffected.

Conclusion Caffeine increases oxygen extraction, suggesting a (transient) stimulating effect on brain metabolism. However, no substantial changes were found in brain perfusion and in electrical brain activity.

Introduction

Apnea of prematurity (AOP) is very common in preterm infants, with a higher incidence amongst lower gestational ages.[1] AOP is defined as a respiratory cessation of at least 20 seconds, or less than 20 seconds and accompanied by a drop in arterial oxygen saturation or bradycardia. AOP is presumably caused by a relative immaturity of the central respiratory control centre. Besides general measurements such as maintaining temperature stability and airway management, methylxanthines are often used to treat AOP. Caffeine is the preferred methylxanthine due to its wide margin of safety and low incidence of side effects.[2] The drug induces respiratory hyperexcitability in several ways, including improvement of minute ventilation, improved diaphragmatic activity, and prevention of hypoxic breathing depression.[3]

The efficacy of caffeine in preventing AOP has been demonstrated extensively.[1] Besides respiratory benefits, the drug also appears to have a neuroprotective effect. The "Caffeine for Apnea of Prematurity" (CAP) study, a large randomized controlled trial comparing caffeine to placebo in very low birth weight infants, showed a positive effect of caffeine on neurodevelopment.[4] At 18 to 21 months follow up, infants who received caffeine treatment showed an improved rate of survival without neurodevelopmental disability, a reduced mortality rate, and a lower incidence of cerebral palsy and of cognitive delay. These results were less clear at 5 years of age, although outcome was still in favour of caffeine.[5] Additionally, caffeine was associated with a reduced rate of developmental coordination disorder.[6] Other studies have also shown favourable effects of early caffeine such as reduced risk of death, bronchopulmonary dysplasia, and patent ductus arteriosus, as well as less time on artificial ventilation.[4,7,8]

At present caffeine is given as respiratory support to infants born <32 week of gestational age (GA) who are not intubated after birth, or to intubated infants who are about to be extubated. If caffeine has a neuroprotective effect, it could potentially be beneficial in other patient groups who currently do not receive caffeine treatment, such as intubated infants or moderately preterm infants born after 32 to 37 weeks of GA. In this study we addressed the effects of caffeine on cerebral oxygenation, perfusion, and electrical brain activity in preterm infants born <32 weeks GA.

Methods

Patients

Preterm infants with a GA of less than 32 weeks and admitted to the neonatal intensive care unit (NICU) of the Wilhelmina children's hospital Utrecht between January and September 2016 who received their first loading dose of 10mg/kg caffeine-base intravenously, were eligible for inclusion. The two indications to start caffeine therapy were: 1) respiratory support in infants who were not intubated on admission or 2) respiratory support in intubated infants ready for extubation. Obstetric and neonatal data were obtained from hospital records. Treatment decisions were made by the attending neonatologist. The Medical Ethical Committee of the University of Utrecht approved the study protocol and waivered parental consent, as both caffeine therapy and neuromonitoring are standard clinical care in our NICU.

Data collection

Neuromonitoring is considered to be standard care during at least the first 72 hours after birth for all preterm infants born <32 weeks GA in the Wilhelmina Children's Hospital, or longer if indicated. It includes cranial ultrasound studies, cerebral oxygenation monitoring with near-infrared spectroscopy (NIRS), and assessment of electrical brain activity with two-channel amplitude integrated electroencephalogram (aEEG). Regional cerebral oxygen saturation ($rScO_2$) was monitored with the INVOS near-infrared spectrometer (Covedien, Mansfield, MA USA) with the small adult sensor (small adult SomaSensor SAFB-SM, Covidien, Mansfield, MA, USA). Fractional tissue oxygen extraction (FTOE) was calculated with $rScO_2$ and arterial oxygen saturation (SaO_2): $(SaO_2 - rScO_2)/SaO_2$. Electrical activity was assessed with a BrainZ aEEG monitor (Natus, Seattle, WA USA). The raw EEG signal of 265Hz was used to calculate spontaneous activity transients (SAT) and the length of intervals between SATs (ISI). The minimal, mean, and maximum amplitudes (min, mean and, max) in μV were derived from the amplitude-integrated EEG signal (aEEG). Repeated cranial ultrasound including Doppler flow assessment were performed and intra- or periventricular haemorrhages were graded according to Papile's classification.[9] Brain perfusion was assessed by the Doppler flow parameters peak systolic velocity (PSV), end-diastolic velocity (EDV) and resistance index (RI) in the anterior cerebral artery (ACA) and internal carotid artery (ICA) before and after caffeine.

Physiological parameters were monitored on a patient monitor (IntelliVue mP70, Philips, Best, NL) and included SaO_2 (%), respiratory rate (RR, in breaths per minute), blood pressure (MABP, in mmHg) and heart rate (HR, in beats per minute). pCO_2 (mmHg)

was collected from routine arterial blood gas analyses. pCO_2 from blood gas analysis had to be taken shortly before and within 4h after caffeine intake. Neuromonitoring data and physiological parameters were simultaneously recorded with BedBase® (software designed for data compilation, University Medical Center Utrecht, The Netherlands) and analysed with SignalBase® (software designed for data analysis, University Medical Center Utrecht, The Netherlands).

Statistical analysis

Ten minute periods of stable and representative data of neuromonitoring (NIRS and aEEG parameters) and physiological parameters were selected before caffeine intake (baseline), during the 30 min infusion period, and every hour after caffeine intake up to 6h, and these periods were used for statistical analysis. Cranial ultrasound data was collected at time points corresponding with baseline measurements and approximately 3h after caffeine intake. pCO_2 data was included when available within the time inclusion criteria. Changes over time were analysed with linear mixed effect model analysis, or paired t-test where appropriate. SPSS (IBM SPSS Statistics for Windows 2012 version 21, Armonk, NY, USA) and Rstudio (RStudio Team 2015 Inc., Boston, MA, USA) were used for statistical analyses, a p-value of <0.05 was considered to be significant. Results are presented as mean(standard deviation), with 95% confidence intervals (95% CI).

Results

In total, 34 preterm infants were included in this study between December 2015 and June 2016. Of these, 32 infants had neuromonitoring data and 27 infants had repeated cranial ultrasounds. In 29 infants, repeated measurements of pCO_2 were available for analysis. All 34 infants received 10mg/kg caffeine-base intravenously, 27 infants for respiratory support following preterm birth and 7 infants for respiratory support to prepare for extubation. The total cohort consisted of more males than females. None of the infants had a hemodynamically significant ductus arteriosus during the study period. All infants had birth weights appropriate for GA. Clinical characteristics are shown in Table 1.

Following caffeine intake $rScO_2$ decreased and cFTOE increased significantly, with partial recovery 6h after caffeine intake. Linear mixed effect analysis showed a significant change in $rScO_2$ and FTOE over time, as shown in Figure 1. An additional predictive effect was found for GA and an interaction between GA and time for both in $rScO_2$ and FTOE. Both HR and MABP increased significantly over time following caffeine administration. Parameters and p-values are shown in Table 2.

Table 1. Clinical characteristics.

	N=34
Male	21 (62%)
Gestational age (wk), mean±SD	28.8±2.1
Birth weight (g), mean±SD	1281±338
Antenatal corticosteroids	22 (65%)
Apgar 5 min, median [range]	8 [2 – 10]
Indication for caffeine therapy • Respiratory support following preterm birth • Respiratory support to prepare for extubation	 27 (79%) 7 (21%)
Age at caffeine administration (h), median [range]	3 [1 – 122]
Respiratory support • None, CPAP or low flow • SIMV or HFO	 23 (68%) 11 (32%)
Respiratory distress syndrome (Surfactant therapy)	16 (47%)
Peri- or intraventricular haemorrhage • None • Mild (grade I/II) • Severe (grade III/IV)	 23 (85%) 3 (11%) 1 (4%)
Seizures	3 (9%)
Hyperbilirubinemia with phototherapy	28 (82%)

Data are n (%), unless otherwise specified. Peri- or intraventricular haemorrhage graded according to Papile's classification.[9] CPAP: continuous positive airway pressure; HFO: high frequency oscillation; SIMV: synchronized intermittend mandatory ventilation.

In the 29 infants with repeated blood gas analysis, a significant decrease was found in pCO_2 following caffeine intake (48.66±6.9 mmHg before, 44.90±7.6 mmHg after; p:0.02). RR and SaO_2 did not change significantly over time. Electrical brain activity was not affected by caffeine intake. SAT rate and ISI were significantly associated with GA, with an increase in SAT rate of 0.33/min per week GA (p<0.001), and a decrease in ISI length of 0.42sec per GA week (p<0.001). Maximal, mean, and minimal amplitude did not change significantly over time after caffeine intake, but were all significantly associated with GA. With every week GA increase, max amplitude increased with 1.44µV (p<0.001), mean amplitude increased with 0.63µV (p:0.001), and min amplitude increased by 0.30µV (p:0.006).

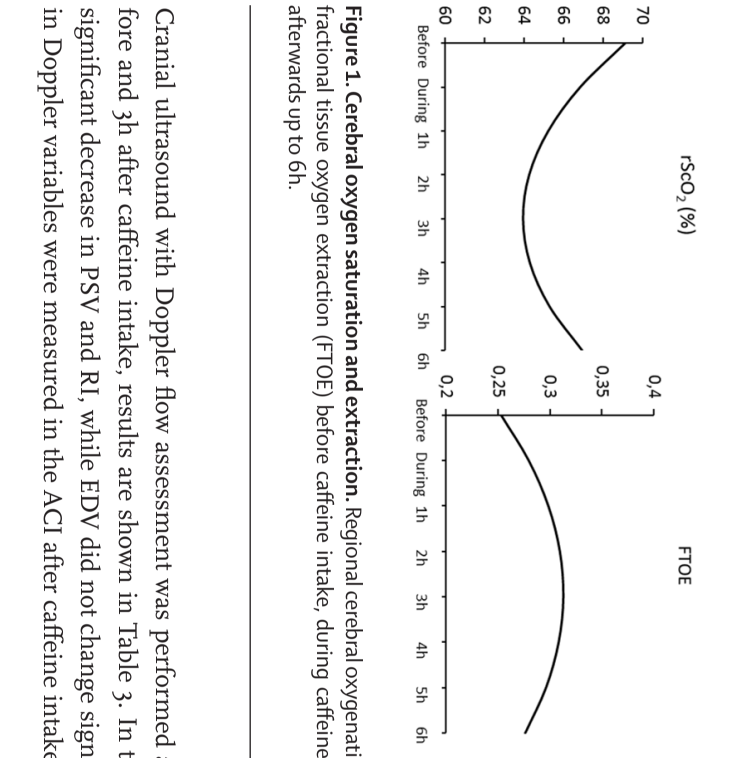

Figure 1. Cerebral oxygen saturation and extraction. Regional cerebral oxygenation saturation ($rScO_2$) and fractional tissue oxygen extraction (FTOE) before caffeine intake, during caffeine infusion, and each hour afterwards up to 6h.

Cranial ultrasound with Doppler flow assessment was performed approximately 1h before and 3h after caffeine intake, results are shown in Table 3. In the ACA, there was a significant decrease in PSV and RI, while EDV did not change significantly. No changes in Doppler variables were measured in the ACI after caffeine intake.

Table 3. Effects of caffeine on cranial ultrasound parameters.

	ACA before	ACA after	p-value	ICA before	ICA after	p-value
Peak systolic velocity (cm/sec)	19.7±7	15.2±6	0.005	28.6±12	23.5±7	ns
End-diastolic velocity (cm/sec)	3.4±3	3.6±2	ns	4.4±4	4.2±2	ns
Resistance index	0.82±0.1	0.75±0.1	0.041	0.85±0.1	0.81±0.1	ns

Doppler parameters before and after caffeine administration. In mean±SD. ACA: anterior cerebral artery; ICA: internal cartotid artery; ns: not significant

Table 2. Mixed model analysis: effects of caffeine on neuromonitoring and vital parameters.

	$rScO_2$ (%)	p-value	FTOE	p-value	MABP	p-value	HR	p-value
Intercept	-0.32 [-54.15 – 53.52]	Ns	1.04 [0.44 – 1.65]	0.0008	31.59 [29.35 – 33.82]	<0.0001	140.4 [136.5 – 144.3]	<0.0001
Time	6.19 [1.20 – 11.18]	0.0165	-0.08 [-0.13 – -0.03]	0.0012	0.37 [0.18 – 0.57]	<0.0001		
$Time_2$	0.33 [0.15 – 0.50]	0.0004	-0.004 [-0.006 – -0.002]	<0.0001			0.09 [0.04 – 0.14]	<0.0001
GA	2.50 [0.56 – 4.33]	0.0145	-0.03 [-0.05 – -0.01]	0.0117				
Time x GA	-0.33 [-0.49 – -0.16]	0.0002	0.004 [0.002 – 0.005]	<0.0001				

Parameters with 95% confidence intervals. FTOE: fractional tissue oxygen extraction; GA: gestational age; HR: heart rate; MABP: mean arterial blood pressure; $rScO_2$: regional cerebral oxygen saturation.

Discussion

Following caffeine treatment in preterm neonates, cerebral oxygen saturation is transiently decreased with increased oxygen extraction, possibly because of an increased metabolism. However, cerebral perfusion and electrical brain activity seem to be unaffected. Caffeine appears to stimulate brain metabolism with increased oxygen consumption, leading to an increased oxygen demand, as indicated by the increase in FTOE and a decrease in $rScO_2$.[10,11] Caffeine can quickly diffuse throughout the body and easily pass the blood brain barrier due to its lipophilic nature.[12,13] The stimulating effects of caffeine on brain metabolism are caused by antagonizing the inhibitory neurotransmitter adenosine by binding the adenosine A1 and A2a receptors.[11] In line with previous research, our study has shown the transient reduction in cerebral oxygenation after caffeine intake.[14, 15] In the study by Tracy et al. cerebral oxygen saturation decreased significantly from 67.7% to 61.3% 1h after caffeine, a decrease of 9.5%, with partial recovery to 64.4% 4h after the dose. FTOE showed a similar increase.[15]

In addition, a reduction in peak systolic blood flow velocity was found in the ACA, a finding also reported in earlier studies on caffeine.[15-17] No changes were detected in the other Doppler indices. This strongly suggested that brain perfusion was not affected by caffeine treatment, which was an unexpected finding. The physiological response to an increase in cerebral metabolism is an increase in brain perfusion.[18] This is a compensating mechanism for the increased oxygen requirement, resulting in an unchanged or rapid recovery of $rScO_2$ and FTOE. However, our findings are line with the results of several other studies on caffeine which were unable to show an effect of caffeine on cerebral blood flow.[19-21] The absence of an increase in cerebral perfusion in response to an increased brain metabolism could have been caused by cerebral vasoconstriction, either by a direct vasoconstrictive effect of caffeine or by antagonising adenosine-regulated vasodilatation.[22] Either mechanism may be supported by a small but significant decrease of the systolic velocity in the ACA, suggesting a change in compliance of the arterial vascular wall.[23] An alternative explanation of the absence of the expected increase in brain perfusion may be a pCO_2–induced vasoconstriction following caffeine intake.[24] Finally, the increased heart frequency and arterial pressure suggest a stimulating effect of caffeine on cardiac function, as reported previously.[25]

Whether these caffeine-induced hemodynamic changes are harmful or not cannot be answered by this study. In neonatal mice models caffeine appears to be protective against hypoxia induced brain injury.[26,27] Moreover, in contrast with other studies that found an increase in amplitudes and continuity following caffeine intake indicative of increased cortical activity, the present study showed no change in electrical brain activity as indicated by the normal aEEG findings, reassuring that no (hemodynamic) deleterious effects occurred on basis of caffeine treatment.[28,29]

Several limitations apply to this study. Caffeine serum concentrations were not quantified during this study, due to its wide safety margin and extensive experience with the drug. Individual caffeine metabolism rates may differ due to immaturity of hepatic enzymes in preterm neonates and standardized dosing regimens may therefore have variable effects.(30) Reported side effects of caffeine include tachycardia, reduced weight gain, tachypnea and hypertension.[31] Occurrence of tachycardia seems to be dose related.[32] FTOE was used as an estimate of oxygen extraction. However, this is a derived parameter from $rScO_2$ and SaO_2, that is not directly measured. Cerebral blood flow was determined indirectly using cranial Doppler ultrasound. Finally, other factors known to have an influence on cerebral blood flow such as cerebral vascular compliance, acceleration time to PSV, and indicators of cardiac performance such as stroke volume and cardiac output were not included in the study design.[23,25]

Conclusion

Caffeine induces a transient significant reduction in cerebral oxygenation with an increase in oxygen extraction, which may be caused by an increase in cerebral metabolism.

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11

Summarizing discussion
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CHAPTER 12

Summarizing discussion
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Summarizing discussion

As survival rates of (extremely) preterm infants keep increasing, so does the number of infants with neurodevelopmental impairment or delay.[1] If we keep pushing the boundaries of viability, it is just as important that we ensure as good an outcome as possible for these infants. The foundation of their development lies in the neonatal period. Injury acquired as a neonate can have a detrimental effect on the rest of the infant's life. But at the same time, there is much to gain during this period. Prevention as well as early recognition of unfavourable cerebral conditions and appropriate interventions are important to improve the infant's health. By monitoring cerebral oxygenation in preterm neonates, it is possible to improve neurological care for unstable and sick newborns in an intensive care setting. Because of its diagnostic and prognostic value it can aid the clinician in assessing the necessity of interventions. By conducting research, we are able to gain a better understanding of the (patho-)physiology of the neonatal brain, to improve clinical care, and thereby improving long-term neurodevelopmental outcome. In our neonatal intensive care unit (NICU), standard clinical care includes a range of of clinical monitoring strategies with a particular focus on neuromonitoring to gain the best possible understanding of the neonates' wellbeing. This includes vital parameters, such as arterial oxygen saturation (SaO_2), heart rate and mean arterial blood pressure (MABP), as well as the monitoring of cerebral oxygenation with the recording of the amplitude-integrated electro-encephalogram (aEEG). In addition, repeated cranial ultrasounds and magnetic resonance imaging (MRI) are performed. With cerebral near-infrared spectroscopy (NIRS) as a measure of cerebral oxygenation integrated into our standard clinical care the neonatologist has a tool to continuously and non-invasively monitor the brain. Cerebral oxygenation is a dynamic process in preterm neonates, constantly under the influence of a variety of factors. The safe range of regional cerebral oxygen saturation ($rScO_2$) is presumed to be between 55-85%. Prolonged exposure to values outside this range has been associated with cerebral injury.[2-4] Moreover, fluctuations in cerebral perfusion and in cerebral oxygenation are thought to be underlying causes of cerebral damage such as intraventricular haemorrhages (IVH) and periventricular leukomalacia (PVL).[5]

This thesis has investigated cerebral oxygenation in the preterm neonate, as monitored with NIRS. In **part I** the practical aspects of NIRS-monitoring are described. The subsequent parts report on the effects of a number of clinical conditions on cerebral oxygenation in preterm neonates in a NICU.

Chapter 2 is an overview of the recent literature regarding the clinical applications of cerebral oxygenation monitoring in the NICU. The peripheral SaO_2 does not always reflect cerebral oxygenation, which makes cerebral oxygenation monitoring with NIRS a

valuable addition to standard monitoring. It is increasingly recognized that direct insight into the brain is important to assess and follow the neonate's condition. The principle of NIRS is based on the absorption of near-infrared light by oxygenated and de-oxygenated haemoglobin within the cerebral tissue, proportionally to their relative concentrations. It is especially suitable in neonates, due to their thin overlying layers of skin and scalp and penetration of the near infrared light into brain areas of interest. Several devices are now commercially available, although differences between sensors remain an issue that must be taken into account during monitoring (see **chapter 3**).[6] The publication of reference values both during transition, immediately after birth, as well as during the first three days have greatly facilitated clinical implementation. Several clinical factors have been shown to affect cerebral oxygenation, such as a hemodynamically significant patent ductus arteriosus (hsPDA), respiratory support, degree of autoregulation of cerebral perfusion, hypotension, being born small-for-gestational-age (SGA), need for transfusion, hypoxic-ischemic encephalopathy, and anaesthesia and surgery. Moreover, cerebral oxygenation has been related to neurodevelopmental outcome. As neurological injury is still common in neonates, especially during the vulnerable period of transition, insight into cerebral oxygenation is a valuable addition to neonatal care.[7]

The increasing use of NIRS to monitor cerebral oxygenation has expanded the commercial market of devices and sensors. Several manufacturers are now offering portable devices, with smaller more flexible sensors designed especially for neonates. In **chapter 3**, we have compared the $rScO_2$ values obtained with five sensors from three different devices. The sensors were the (small) adult (SomaSensor SAFB-SM), neonatal (Oxyalert CNN) and pediatric sensor (SomaSensor SPFB) by INVOS 5100C Somanetics (Covidien, Troy, MI), the neonatal sensor (small sensor) by Fore-Sight (CAS Medical Systems, Branford, CT) and the adult Equanox sensor (Classic Sensor 8000CA) by NONIN (NONIN Medical, Plymouth, MN). Infant were monitored bilaterally with two different sensors for at least one hour, after which the sensors were switched to the contralateral side for another monitoring period of one hour. Overall, there was a good correlation between the sensors (linear regression coefficient between 0.62 – 0.89). However, substantial differences existed between the results of individual sensors, where the smaller (pediatric and neonatal) sensors measured between 10 – 16% higher than the larger (adult) sensors. Caution is warranted when interpreting values as 'hypoxic' with the smaller sensors. At the same time, variation is lost in the higher regions as the cut-off value of the device with smaller sensors is set to 95%, resulting in a flat line where trends are no longer visible. Therefore, we recommend that the type of sensor must be taken into account when implementing cerebral oxygenation monitoring.

One of the major limitations of the clinical implementation of cerebral oxygenation monitoring was a lack of reliable reference values, based on a large cohort of infants with different gestational ages (GA). In **chapter 4** we analysed the course of $rScO_2$ and fractional tissue oxygen extraction (FTOE) during the first 72 hours after birth in 999 preterm infants. $rScO_2$ follows a slight parabolic curve, with an increment in offset with increasing GA. Reference value graphs are provided with the mean $rScO_2$ and percentile lines per GA group (24-25, 26-27, 28-29 and 30-31 weeks of gestation). Similar graphs are provided for FTOE. These reference values graphs facilitate bedside interpretation of cerebral oxygenation, while taking GA into account. The reference values were obtained with the small adult sensor (SomaSensor SAFB-SM, Covidien) in combination with INVOS NIRS monitor (INVOS 4100 or 5100(c); Covidien, Mansfield, MA). Our previous research had shown that neonatal sensors measure higher values when compared to the adult sensors (**chapter 3**).[6] To facilitate the use of reference values regardless of sensor type, we built a conversion diagram for the neonatal sensor and provided reference graphs. In addition, we analysed the effect of postnatal age (PNA), a hsPDA, gender, and birth weight. $rScO_2$ is lower in female neonates than in males, and may decrease in case of a hsPDA. $rScO_2$ is higher with advancing PNA and GA, in male neonates, and in infants born SGA compared to appropriately grown peers.

In **part II**, the effect of a hsPDA on cerebral oxygenation is explored further. The ductus arteriosus is the vascular channel connecting the main pulmonary artery and the aorta, which enables redirection of the pulmonary blood flow in utero away from the pulmonary circulation to the descending aorta and the placenta. Low oxygen tension and vasodilatatory prostaglandins (PG) maintain fetal ductal patency. After birth, increased oxygen tension and reduction in PGs induce vasoconstriction in the ductal smooth muscle cells, with functional closure as a result. Ductal intramural hypoxia induces vascular remodelling, leading to permanent anatomic closure. Failure of ductal closure is common in preterm infants, with a higher incidence at a lower GA.[8] Many mechanisms that promote ductal closure are immature in preterm infants. For instance, ductal sensitivity to oxygen is reduced whilst PG sensitivity in increased, and the production of nitric oxide (NO), a potent vasodilator, is maintained after birth in preterm infants. Left-to-right shunting through the open duct causes pulmonary overflow with systemic hypoperfusion.[9] This ductal steal effect also affects cerebral perfusion.[10,11] $rScO_2$ is reduced and FTOE is increased in infants with a hsPDA, where infants who eventually require surgical duct ligation are the most severely affected.[12,13] This is an important finding since the developing brain is particularly vulnerable to disturbances in perfusion and oxygenation.

The hemodynamic impact of ductal shunting on cerebral oxygenation may be variable, as both cerebral oxygenation and ductal shunting are dynamic features. In **chapter 5** we conducted a prospective observational study to analyse the association between echocardiographic parameters, cerebral oxygenation, and a hsPDA. Three serial echocardiographic examinations were performed in 380 preterm infants on the second, fourth, and sixth day after birth by pediatric cardiologists. Cerebral oxygenation was monitored before each echocardiographic examination, and a baseline period was selected. $rScO_2$ was shown to be significantly associated with ductal diameter measured by echocardiography over time, where a larger diameter resulted in a reduced cerebral oxygenation. To assess a possible association between $rScO_2$ and the hemodynamic significance of the duct (as an indication of the degree of flow through the duct) over time, infants were divided into four groups: 1) the duct was closed, 2) the duct was open but hemodynamically non-significant (non-sPDA, i.e. did not receive treatment during the entire study period), 3) a hsPDA requiring treatment that was successfully closed during the study period (SC hsPDA), or 4) a hsPDA requiring treatment that was unsuccessfully closed at the end of the study period (UC hsPDA). $rScO_2$ takes a different course over time, depending on the status of the duct. At day 6, infants with a SC hsPDA showed the highest values of $rScO_2$, whereas infants with an UC hsPDA had the lowest cerebral oxygenation values. Low or decreasing cerebral oxygenation values can be indicative of a hsPDA. As there is still a considerable debate concerning the diagnosis of hsPDA, the assessment of the cerebral effects of an open duct with NIRS monitoring can be of help to the clinician.

Intra-uterine growth retardation induces fetal redistribution of blood flow to spare the perfusion to the most vital organs such as the brain, at the expense of other organ systems such as intestines and kidneys. This increased cerebral perfusion is described as the "brain-sparing" effect. As a result, SGA infants show higher values of $rScO_2$ during the first days after birth.[14,15] Therefore, SGA infants might be protected against the adverse effects of a hsPDA on the cerebral oxygenation. The effect of a hsPDA on the cerebral oxygenation in preterm SGA neonates was compared to that of appropriately-grown (AGA) infants in **chapter 6**. $rScO_2$ and FTOE were continuously monitored in 36 SGA infants with and without a hsPDA, and in 36 matched AGA infants with and without a hsPDA, resulting in 4 patient groups. $rScO_2$ was significantly lower in infants with a hsPDA. Unexpectedly, this effect was more pronounced in SGA infants, where a significant decline in $rScO_2$ was seen with advancing PNA. These results question the notion that the "brain-sparing" effect is a protective mechanism. Even though they had higher initial $rScO_2$'s, SGA infants appeared to be more severely affected by the adverse effects of the open duct on the brain. A limited autoregulatory capacity due to cerebrovascular remodelling in utero could be an underlying cause. Early hsPDA diagnosis and treatment may be even more beneficial in SGA infants.

Patency of the ductus arteriosus is a complex mechanism involving several vasodilative agents. As mentioned earlier, the most important are PG and NO. However, carbon monoxide (CO) also seems to play a role. CO is produced in the ductal wall by haemoxygenase, and its production is upregulated by pro-inflammatory cytokines.[16] Moreover, CO is a marker of inflammation and oxidative stress. This could indicate that early inflammation induces endogenous CO production, resulting in a relaxation of the duct, eventually leading to ductal steal and a reduction in cerebral oxygenation. In **chapter 7** we report on the association between early CO measurements (within 24 hours after birth), ductal patency, and $rScO_2$ in 91 preterm infants. CO can be measured in exhaled air as end-tidal CO, corrected for ambient CO (etCOc). $rScO_2$ was not related to etCOc on the first day of life. Also, $rScO_2$ did not differ between infants who developed a hsPDA when compared to infants who did not at this early stage. The large number of hemodynamic changes during the transitional phase early in life could prevent detection of any effects of etCOc on the cerebral oxygenation. However, etCOc was significantly higher in infants who developed a hsPDA. A cut-off value of 2.5ppm gives a positive predictive value of 55%, while a negative predictive value of 88% is found. This indicates that early low etCOc values can be used as prognostic marker to assess the risk of hsPDA.

There is an ongoing debate whether or not to treat a hsPDA. Although a hsPDA has been associated with several morbidities, treatment in itself might also have a negative effect on the neonate.[17] The influence of a hsPDA on long-term neurological outcome would aid in the decision to treat, however relevant studies are scarce and generally only report on outcome up to 2 years of age. In **chapter 8** we have analysed neurodevelopmental outcome in 78 infants born before 28 weeks GA. They were divided into 3 groups, based on the treatment of their hsPDA: 1) no treatment; 2) treatment with indomethacin; 3) surgical ligation of the ductus. Outcome was assessed at 2 years of age with the Dutch Bayley Scales of Infant and Toddler Development 3rd Edition (BSITD-III-NL) and at 5 years with the Movement Assessment Battery for Children 2nd Edition (M-ABC-2) and the Dutch Wechsler Preschool and Primary Scale of Intelligence 3rd Edition (WPPSI-III-NL). Ductal treatment increased the risk of poor motor outcome at 5 years of age, although not significantly in a multivariate analysis. Ductal surgery was significantly related to poor cognitive outcome at 5 years of age, in the adjusted odds ratios. In addition, $rScO_2$ was lower before the start of treatment in infants with a poor cognitive outcome. These results indicate that exposure to lower cerebral oxygenation levels and ductal surgery negatively affect neurological outcome. Cerebral oxygenation monitoring might thus identify infants at risk of poor cognitive outcome at pre-school age.

The effects of carbon dioxide (CO_2) on the neonatal brain are discussed in **part III**. CO_2 is one of the main mediators that affect cerebral perfusion and oxygenation. Hypercapnia induces cerebral vasodilatation, whereas hypocapnia induces vasoconstriction. This effect is mainly caused by a change in perivascular pH, as CO2 can easily cross the blood-brain barrier. After chronic CO2 abnormalities, pH will normalize by buffer capacity with restoration of cerebral blood flow (CBF).[18] For example, hypercapnia increases the H+ concentration, resulting in relaxation of cerebral vascular smooth muscle cells of the vessels with cerebral vasodilatation.[19] Inversly, hypocapnia induces vasoconstriction. Both hyper- and hypocapnia have been associated with neonatal brain injury. Hypercapnia, by inducing vasodilatation, increases cerebral perfusion with increased risk of IVH. Moreover, autoregulation may be diminished in vessels dilated by hypercapnia, leading to impaired vascular responses, e.g. to hypoxia. Hypocapnia, by inducing vasoconstriction, reduces CBF and thus increases the risk of ischemic injury. Fluctuations in CO_2 also seem to have negative effects on the neonatal brain, as they are related to severe IVH and increased risk of neurodevelopmental impairment or death.[20,21]

In **chapter 9**, we have evaluated the effects on the neonatal brain of acute fluctuations in end-tidal CO_2 ($etCO_2$), as a marker of arterial pCO_2. Fluctuations in pCO_2 are common in preterm infants, often caused by respiratory variations due to pulmonary disease. In this study, we included all mechanically ventilated infants on $etCO_2$ monitoring and neuromonitoring by NIRS and aEEG, who showed fluctuations of at least 5mmHg CO_2 during the first 3 days after birth. Ten minute periods of stable monitoring were selected before, during, and after the change in $etCO_2$. In a total of 38 infants, 60 episodes of an acute increase in $etCO_2$ and 70 episodes of an acute decrease in $etCO_2$ were identified. During an acute increase in $etCO_2$, $rScO_2$ increased with a decrease in FTOE. The electrical brain activity on aEEG diminished, with a reduction in the number of spontaneous activity transients (SAT) per minute, as a measure of brain activity, and an increase in the length of the interval between SATs (interSAT interval, ISI). An acute decrease in $etCO_2$ resulted in a decrease in $rScO_2$ with an increased FTOE. A small increase in electrical brain activity was found, as indicated by an increase in SATs/min. These results indicate that arterial pCO_2 fluctuations, even within the normal range, directly affect the neonatal brain. It is important for clinicians to be aware of these effects, especially in ventilated infants. Intermittent pCO_2 determinations by blood gas analysis may not be sensitive enough to detect these fluctuations. Cerebral oxygenation monitoring is an important additional tool to detect and limit the disturbances in oxygenation induced by fluctuations in arterial CO_2.

Hypercapnia has a depressant effect on the central nervous system in adults, and can even induce coma. In **chapter 10**, we analysed the effects of severe hypercapnia on the neonatal brain, assessing both cerebral oxygenation and electrical brain activity. Severe hypercapnia was defined as pCO_2>70mmHg and diagnosed with blood gas analysis. Repeated routine blood gas analysis are generally performed every 4 hours in our NICU. Twenty-five infants were included with 32 episodes of severe hypercapnia. During episodes of severe hypercapnia, electrical activity was severely diminished, with a reduction in SATs/min and an increase in ISI length. A depression of the aEEG background pattern, indicating a decrease in electrical brain activity, was found in 84% of the episodes. The background pattern recovered after pCO_2 normalized. At the same time $rScO_2$ increased and FTOE decreased; these effects, however, were not significant. In **chapter 9** we showed that acute fluctuations in arterial of pCO_2 did have a significant effect on $rScO_2$, where the magnitude of the changes as well as the baseline level pCO_2 do not have an effect. It is a possible that the hypercapnia was present long enough to initiate the buffering responses that normalize cerebral perfusion and oxygenation, since the severe hypercapnic events were diagnosed by blood gas analysis. The respons of electrical brain activity (aEEG) appears to be much increased during severe hypercapnia as compared to acute fluctuation in pCO_2 of at least 5mmHg, as was shown by the background pattern deteriorating into burst suppression or even a flat trace. Acute fluctuations in pCO_2 have an effect on both cerebral oxygenation and electrical activity, where more permanent severe hypercapnia seems to have a greater effect on electrical activity of the brain.

In **part IV**, the effects of caffeine on the neonatal brain are examined. One of the most commonly used drugs in the NICU is caffeine. It is used to reduce apnea of prematurity (AOP), a frequent complication in preterm infants. The incidence of AOP is directly related to GA, with an incidence reaching 100% amongst the lowest GA's.[22] Due to its lipopholic nature, caffeine can easily pass the blood-brain barrier to reach the brain, where it acts as an adenosine antagonist by binding the adenosine A1 and A2a receptors.[23-25] Adenosine is an inhibitory neurotransmitter.

The results of a large multicentre randomized controlled trial comparing caffeine to placebo (the CAP trial) indicated that caffeine may have a neuroprotective effect.[26] Infants with caffeine in the neonatal period had a lower mortality rate and a higher survival rate without neurodevelopmental delay with a reduction in cerebral palsy and an improved cognitive outcome. In **chapter 11** we analysed the effects of caffeine for AOP on the neonatal brain in 34 preterm infants. Brain assessment included recording of cerebral oxygenation with NIRS and electrical brain activity with (a)EEG, and measuring of brain perfusion with Doppler cranial ultrasound. Cerebral oxygenation and electrical brain activity monitoring was initiated before the administration of caffeine and continued up

to 6 hours after the infusion. Cranial ultrasound scanning was performed before and within 3 hours after caffeine administration. pCO_2 values were included in the analysis if infants had a blood gas sample taken before and shortly after caffeine. $rScO_2$ decreased significantly after caffeine administration with a nadir at 1 hour, coinciding with a significant increase in FTOE. Surprisingly, the Doppler peak systolic flow velocity (PSV) decreased significantly in the anterior cerebral artery. We expected an increase in perfusion following the increase in cerebral oxygen metabolism. End-diastolic flow velocity was not affected, and neither were the velocity parameters in the internal carotid artery. The decrease in PSV might be explained by a vasoconstrictive effect of caffeine, negating the vasodilatatory effect of adenosine. Alternatively, vasoconstriction could be induced by the significant reduction in pCO_2 that was seen in infants where pCO_2 values were available. No differences were found in aEEG or EEG-derived parameters, ensuring the reduction in PSV had no detrimental effects on cerebral function. Heart rate and MABP increased significantly and consistently over time after caffeine. Caution is warranted with interpreting the potential neuroprotective effect of caffeine, as it seems to induce a (transient) reduction in cerebral oxygenation.

Conclusion

It is increasingly recognized that direct insight into the brain of preterm neonate is important to assess and follow the neonates condition, ascerebral oxygenation can be at risk. Neurological injury is still common in neonates, especially during the vulnerable period of transition. Monitoring arterial oxygen saturation is not sufficient as it does not always reflect cerebral oxygen saturation. **Part I** has shown the importance of neonatal NIRS monitoring. When interpreting reference values, gestational age, postnatal age, gender, patent ductus arteriosus and birth weight are important factors of influence, as well as type of device and sensor. In **part II** we showed that a patent ductus arteriosus affects cerebral oxygenation, especially in small for gestational age infants, and affects long-term neurological outcome. On echocardiography, cerebral oxygenation is most related to ductal diameter. Carbon monoxide might be a potential predictor of a patent ductus arteriosus. **Part III** has focused on the effects of CO_2, where acute fluctuations in CO_2 affect both cerebral oxygenation and electrical brain activity. Severe hypercapnia seems to have a more profouned effect on electrical brain activity. In **part IV**, caffeine has a transient reducing effect on cerebral oxygenation shortly after administration. In conclusion, monitoring of cerebral oxygenation with near-infrared spectroscopy is of important added value in a neonatal intensive care setting.

Future research

In this thesis, we have shown that cerebral oxygenation is a dynamic feature under the influence of several clinical factors. One of the most important questions is if unfavourable or fluctuating cerebral oxygenation can be identified and prevented with NIRS monitoring. In the study by Pichler et al, visible $rScO_2$ monitoring with NIRS to guide respiration and supplementary oxygen therapy during transition immediately after birth was compared to blinded $rScO_2$ monitoring.[27] The burden of hypoxia was reduced with more than 50% in infants with visible $rScO_2$. In addition, the SafeBoosC study (Safeguarding the brains of our smallest children) analysed the effect of visible versus blinded $rScO_2$ monitoring during the first 3 days of life in preterm infants in a multicentre randomized controlled trial.[28] Infants with visible $rScO_2$ monitoring were significantly less exposed to unfavourable $rScO_2$ values compared to infants with blinded NIRS registration. These results demonstrate that hyper- and hypoxia can indeed be recognized and that $rScO_2$ monitoring with NIRS can indeed be used to improve cerebral oxygenation stability. An additional treatment protocol involved several steps to detect the underlying cause and apply appropriate treatment to restore oxygenation. This supports our conviction that cerebral oxygenation monitoring is a vital part of neonatal care and can indeed improve cerebral health. Awareness of which factors affect oxygenation and how is an essential part of the implementation of cerebral oxygenation monitoring.

It is important to know if stabilizing cerebral oxygenation indeed results in an improved neurological outcome. It has already been demonstrated that $rScO_2$ has predictive value for neurodevelopmental outcome in infants with birth asphyxia.[29] In addition, Alderliesten et al have shown that cerebral oxygenation <55% during the first 3 days of life is associated with adverse neurodevelopmental outcome at both 15 and 24 months of age, with an important predicting effect for percentage of time spent below the threshold (personal communication). Even percentage of time spent below ±1SD according to the reference values were related to adverse neurodevelopmental outcome, indicating a GA specific approach of "abnormal" values. In the SafeBoosc study, a trend towards reduction in mortality and severe brain injury was seen.[28] This effect did not reach statistical significance, although it should be taken into account that the study was not powered for this. Large randomized controlled trials into short- and longterm outcome after cerebral oxygenation monitoring are much needed.

In this thesis, we have identified a number of clinical conditions that can alter cerebral oxygenation. There are, however, several other settings where monitoring could make a difference. For instance, $rScO_2$ can be used to calculate cerebral autoregulation. Studies have shown that cerebral autoregulation can be especially impaired in sick and unstable infants, putting them at increased risk of cerebral injury.[30] Future research will focus on the application and interpretation of autoregulation, calculated in real time at the bedside, to evaluate the condition of the neonatal brain as well as vulnerability to injury. Another important issue that need answers is what the optimal value is for MABP and what should be considered hypotension. An arbitrary cut-off value based on GA seems insufficient to predict outcome.[31] A tool to assess the end-organ perfusion and oxygenation at different blood pressures might bring us one step closer in identifying 'true' hypotension.

The monitoring of cerebral oxygenation is one way to asses s a neonatal brain, together with (a)EEG monitoring, cranial ultrasound, MRI and vital parameters such as SaO_2, heart rate and MABP. Future research and advances in technology should allow for integration of all these parameters, to design algorithms and other mathematical models to predict risks and outcomes. Data is now being collected prospectively from nearly all infants administered at the NICU. Analysis of these "Big Data" should result in prediction models, tailored to patient specific characteristics, and improve patient care by a more individual approach.[32,33]

In NICU, infants are often extensively monitored. User-friendliness of patient monitoring could be increased. If different parameters can be collected together by one monitoring device, the number of screens at the bedside can be reduced. Wireless connections between sensors and the monitor increase mobility of the patient, facilitating both clinical care for medical practitioners as well as access for the parents. A NICU admission is a stressful experience for both patients and parents. Facilitating physical contact between parents and their infants, for instance with Kangaroo care where there is skin-to-skin contact between parent and neonate, can reduce stress levels and improve bonding.[34] Kangaroo care has beneficial effects on several clinical parameters such as discomfort, sleep, and length of hospital stay.[35-37] Improving user-friendliness of monitoring devices is an important issue, although research in this area is scarce.

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12

Nederlandse samenvatting

13

CHAPTER 13

Nederlandse samenvatting

Cerebrale oxygenatie van de vroeggeborene

Een van de belangrijkste redenen om zuurstof in de hersenen te onderzoeken bij premature neonaten is om een beter beeld te krijgen van de (patho-)fysiologie van het brein, om de zorg te kunnen optimalizeren en daarmee de uitkomst op lange termijn te verbeteren. Het aantal kinderen dat te vroeg geboren wordt neemt toe, en daarmee het aantal kinderen met neurologische schade.[1] Het is belangrijk om deze kinderen de beste zorg te kunnen bieden. Schade in het brein die wordt opgelopen in de neonatale periode kan een grote invloed hebben op de kwaliteit van leven. Het voorkomen alsmede vroegtijdig herkennen van ongunstige zuurstof saturatie in het brein kan helpen schade te voorkomen. Het meten van zuurstof in de hersenen met near-infared spectroscopy (NIRS) is geïntegreerd in de dagelijkse zorg, tegelijkertijd met het meten van cerebrale functie met electro-encefalogram (EEG), het monitoren van de hartslag, de perifere arteriële zuurstof saturatie en de bloeddruk. Daarnaast wordt regelmatig het brein in beeld gebracht door middel van echografie en MRI. Met NIRS kan de zuurstof in de hersenen continu en non-invasief gemeten worden. De veilige "range" van cerebrale zuurstof saturatie wordt geschat op 55-85%. Langdurende blootstelling aan waardes buiten deze range is geassocieerd meteen minder goede cognitieve en neurologische ontwikkeling.[2-4] Daarnaast kunnen fluctuaties de doorbloeding en zuurstofvoorziening ook leiden tot schade.[5] Zuurstofvoorziening van de hersenen is een dynamisch proces, continu onder de invloed van meerdere factoren. In dit proefschrift is onderzoek gedaan naar welke factoren invloed hebben op de zuurstofvoorziening van de hersenen in te vroeg geboren neonaten. In **deel I** komen de technische aspecten van monitoren met NIRS aan bod.

Hoofdstuk 2 is een overzicht van de recente literatuur over de klinische toepasbaarheid van meten van de zuurstofvoorziening van de hersenen. Monitoren van de zuurstofvoorziening is van toegepaste waarde in de neonatologie, aangezien arteriële saturatie vaak geen betrouwbare weergave is van de zuurstofvoorziening van het brein. De NIRS-machine stuurt via een sensor, bevestigd op het hoofd, een bundel licht uit in het bijna-infrarode spectrum door het hersenweefsel, waar het wordt geabsorbeerd door geoxygeneerd en gedeoxygeneerd hemoglobine, waarna de relatieve concentraties worden berekend. Door een dunne overliggende huid en schedel is deze techniek met name toepasbaar bij neonaten. Er zijn verschillende apparaten en sensoren op de markt beschikbaar, waardoor tijdens metingen altijd rekening moet worden gehouden met het type sensor (zie **hoofdstuk 3**). Referentiewaarden gecorrigeerd voor leeftijd en zwangerschapsduur zijn inmiddels gepubliceerd. De zuurstofsaturatie in de hersenen wordt beïnvloed door een hemodynamisch belangrijke open (patent) ductus arteriosus, ademhaling ondersteuning, hypotensie, groeiachterstand van de pasgeborene, anemie, perinatale asfyxie en tijdens neonatale chirurgie onder anesthesie.Het verloop van de zuurstofvoorziening van

hersenen in de neonatale periode lijkt gerelateerd aan de ontwikkeling op latere leeftijd. Aangezien neurologische schade nog vaak voorkomt bij neonaten, is het meten van de zuurstofconcentratie in de hersenen van toegevoegde waarde.[6]

In **hoofdstuk 3** zijn verschillende NIRS apparaten en bijbehorende sensoren met elkaar vergeleken in 55 neonaten. Nieuwe, kleinere sensoren speciaal voor gebruik bij neonaten zijn vergeleken met voorgaande sensoren voor gebruik in volwassenen. Hoewel de correlatie tussen sensoren over het algemeen goed was, bestonden er toch verschillen in de gemeten waarden. De neonatale sensoren meten gemiddeld tussen de 10 en 16% hoger dan de volwassenen sensoren. Voorzichtigheid is geboden bij de interpretatie van de waarden.

In **hoofdstuk 4** zijn referentiewaarden gepresenteerd voor te vroeg geboren neonaten gedurende de eerste 72 uur na de geboorte, gebaseerd op 999 te vroeg geborenen. Een extra onderscheid is gemaakt voor zwangerschapsduur. Referentiegrafieken voor zowel de volwassen- als de neonatale sensor zullen de interpretatie van de zuurstofsaturatie in de hersenen in de couveuse vergemakkelijken. Daarnaast is het effect van een open ductus arteriosus, geslacht en geboortegewicht geanalyseerd.

In **deel 2** wordt verder ingegaan op de invloed van een open ductus arteriosus op de zuurstofvoorziening van de hersenen. De ductus arteriosus verbind de aorta met de pulmonale slagader. Lage zuurstofspanning en circulerende prostaglandines houden de ductus open voor de geboorte. Na de geboorte stijgt de zuurstofspanning en dalen de prostaglandines, waardoor de ductus moet sluiten. In te vroeg geboren baby's zijn veel van deze mechanismes nog niet voldoende ontwikkeld en blijft de ductus arteriosus open. Hierdoor stroomt bloed van de systemische- naar de longcirculatie, met een negatief effect op de doorbloeding van de hersenen.[7-9] Een daling van de zuurstofsaturatie en toename in zuurstofextractie in het brein is aangetoond in kinderen met een open ductus arteriosus, waarbij kinderen die een chirurgische ductus sluiting nodig hebben hiervan de meeste last ondervinden.[10,11] Het ontwikkelende brein is gevoelig voor verstoring in de doorbloeding en daarmee de zuurstofvoorziening.

In **hoofdstuk 5** is de relatie tussen echocardiografische parameters en de zuurstofsaturatie in de hersenen in neonaten met en zonder een open ductus arteriosus onderzocht. In 380 te vroeg geboren neonaten werd 3 keer per week een echocardiografie vervaardigd van het brein en werd de zuurstofsaturatie in de hersenen gemeten. De diameter van de ductus arteriosus, gemeten met echocardiografie, was sterk geassocieerd met de zuurstofsaturatie in de hersenen, waarbij een grotere diameter een daling van de zuurstofsaturatie indiceert. Om de ernst van de ductus arteriosus te bepalen werden kinderen

verdeeld in 4 groepen: 1) gesloten ductus; 2) hemodynamisch niet belangrijke ductus; 3) succesvol behandelde en gesloten hsPDA; 4) hsPDA die nog open en hemodynamisch belangrijk was aan het einde van de studie periode. De status van de ductus arteriosus beïnvloed het verloop van de zuurstofsaturatie in de hersenen over de tijd. Een daling in de zuurstofsaturatie in de hersenen kan mogelijk wijzen op een open ductus arteriosus.

Intra-uteriene groei vertraging kan leiden tot aanpassing van de perfusie naar de meest belangrijke organen, waaronder het brein. Deze verhoogde doorbloeding van de hersenen leidt tot verhoogde zuurstofsaturatie in het brein na de geboorte, in kinderen met een te laag geboortegewicht.[12,13] Hierdoor zouden zij mogelijk beter beschermd tegen de negatieve cerebrale effecten van een open ductus arteriosus. Echter, in tegenstelling tot onze hypothese, hebben we in **hoofdstuk 6** aangetoond dat de daling van de zuurstofsaturatie in het brein door een open ductus arteriosus het sterkst was in kinderen met een te laag geboortegewicht. Vroege opsporing en behandeling van open ductus arteriosus kan extra voordelen hebben in deze patiëntengroep.

De ductus blijft open onder invloed van verschillende complexe mechanismes. Koolstof monoxide (CO) lijkt hierin ook een rol te spelen. CO wordt geproduceerd in de ductus, en is daarnaast een marker van oxidatieve stress en inflammatie.[14] Vroege inflammatie zou de productie van CO kunnen stimuleren, en daarmee de ductus arteriosus open houden. In **hoofdstuk 7** is de concentratie CO in uitgeademde lucht gemeten (binnen 24 uur na geboorte) en de zuurstofsaturatie in de hersenen in 91 te vroeg geboren neonaten gemeten. De zuurstofsaturatie in de hersenen had geen relatie met de CO concentratie op de eerste dag na de geboorte, en was niet anders in kinderen die wel of geen open ductus arteriosus ontwikkelden. De concentratie CO was wel significant hoger in kinderen die een open ductus arteriosus ontwikkelden, waarbij een afkapwaarde van 2,5ppm de beste sensitiviteit en specificiteit gaf. Vroege CO meting zou mogelijk gebruik kunnen worden als een indicator voor het ontwikkelen van een open ductus arteriosus.

Er is toenemend discussie over het wel of niet behandelen van een open ductus arteriosus. Hoewel een open ductus arteriosus is gerelateerd aan diverse complicaties, de behandeling zelf is ook niet zonder risico.[15] In **hoofdstuk 8** is de relatie tussen de behandeling van een open ductus arteriosus en de uitkomst op 2-jarige en op 5-jarige leeftijd geanalyseerd in 78 premature neonaten. De neonaten werden in 3 groepen verdeeld: 1) geen ductus behandeling ondergaan; 2) medicamenteus behandelde ductus; 3) chirurgisch gesloten ductus. De behandeling van een patente ductus arteriosus was geassocieerd met afwijkende motorische uitkomst op 5 jarige leeftijd, maar bleef niet significant in multivariate analyse. Chirurgische ductus sluiting was geassocieerd met afwijkende cognitieve uitkomst op 5-jarige leeftijd, ook na correctie voor verschillende factoren.

Daarnaast was de zuurstofsaturatie in de hersenen voor het starten van de behandeling lager in kinderen met een afwijkende cognitieve uitkomst. Verlaagde zuurstofsaturatie in de hersenen en chirurgische ductus sluiting hebben een negatief effect op de cognitieve uitkomst op 5 jaar. Het monitoren van de zuurstofsaturatie in de hersenen met NIRS in de neonatale periode kan mogelijk bijdragen aan het identificeren van deze kinderen

In **deel 3** zijn de effecten van koolstof dioxide (CO_2) op het neonatale brein onderzocht. CO_2 heeft een belangrijk effect of de doorbloeding en zuurstofvoorziening van de hersenen. Bij hypercapnie (hoge pCO_2) kan CO_2 makkelijk de bloed-hersenen barrière overbruggen, en daar de perivasculaire pH veranderen met relaxatie van de gladde spiercellen en vaatverwijding tot gevolg.[16] Uiteindelijk zal de buffercapaciteit ervoor zorgen dat het evenwicht zich weer hersteld.[17] Zowel hypo- (lage pCO_2) als hypercapnie zijn geasso-cieerd met schade in het brein. Hypercapnie induceert vaatverwijding met risico op bloedingen in het brein. Bovendien kan autoregulatie van de hersenen (belangrijk voor een stabiele hersendoorbloeding) beperkt zijn in vaten die al verwijd zijn door hypercapnie. Hypocapnie induceert vaatconstrictie, met risico op ischemische schade. Niet alleen extreme waarden, maar ook schommeling in CO_2 zijn gerelateerd aan bloedingen, neurologische schade of overlijden.[18,19]

In **hoofdstuk 9** zijn de effecten van acute CO_2 fluctuaties op het neonatale brein geanalyseerd. CO_2 is continu gemeten in de uitgeademde lucht ($etCO_2$) als een marker voor pCO_2. Fluctuaties in pCO_2 komen vaak voor in te vroeg geboren neonaten, meestal door respiratoire oorzaken. In deze studie zijn alle beademde te vroeg geboren neonaten geincludeerd die hersenbewaking met NIRS en aEEG hadden en $etCO_2$ fluctuaties van tenminste 5mmHg gedurende de eerste 3 dagen na geboorte.. Periodes van 10 minuten werden geselecteerd voor, tijdens en na de $etCO_2$ fluctuatie. In totaal zijn er 38 patiënten geïncludeerd, met 60 episodes van acute $etCO_2$ stijging en 70 episodes van acute $etCO_2$ daling. Tijdens acute $etCO_2$ stijging, nam de zuurstofsaturatie in de hersenen toe met een daling in zuurstofextractie, terwijl de elektrische activiteit van het brein op het aEEG nam af. Tijdens de acute $etCO_2$ daling nam de zuurstofsaturatie in de hersenen af met een stijging in zuurstofextractie, met een kleine stijging in de elektrische activiteit van het brein. Deze resultaten tonen aan dat fluctuaties in CO_2, zelfs binnen de normale grenzen, een direct effect hebben op het neonatale brein. Het is belangrijk dat de neonatoloog op de hoogte is van deze effecten, met name in beademde kinderen. Intermitterende bloedgasanalyses zijn mogelijk niet afdoende om alle abnormale pCO_2 waarden te detecteren. Het monitoren van zuurstofsaturatie in de hersenen is een belangrijk aanvullend middel om deze verstoringen te detecteren en herstellen, zodat de negatieve effecten van CO_2 fluctuaties op het brein beperkt worden.

Hypercapnie heeft een inhiberend effect op het brein, en kan in volwassenen zelfs tot coma leiden. In **hoofdstuk 10** zijn de effecten van ernstige hypercapnie op het neonatale brein onderzocht, waarbij zowel de zuurstofsaturatie als elektrische activiteit van het brein is geanalyseerd. Hypercapnie was gedefinieerd als pCO_2 >70mmHg tijdens bloedgas analyse. Bloedgas analyses worden standaard om de 4 uur verricht in onze neonatale intensive care unit. In totaal werden 25 neonaten geïncludeerd, met 32 episodes van ernstige hypercapnie. Elektrische hersenactiviteit was sterk verminderd tijdens ernstige hypercapnie: zich uitend op het aEEG als een daling van episoden van spontane activiteit en een verlenging van de episoden met weinig tot geen activiteit. Een depressie van het achtergrondpatroon op het aEEG werd in 84% van de episodes gevonden. Het achtergrondpatroon herstelde zich na normalisatie van de pCO_2. Een toename in zuurstofsaturatie en daling in zuurstofextractie in het brein werd gevonden, maar deze effecten bereikten niet de statistische significantie. Zoals hierboven beschreven, reageert zuurstofsaturatie van de hersenenop acute fluctuaties in CO_2, waarbij de hoogte van de fluctuatie en de uitgangswaarde voor de fluctuatie niet van invloed waren (zie **hoofdstuk 9**). Aangezien de hypercapnie gediagnosticeerd werd met bloedgas analyse, is het mogelijk dat de hypercapnie al enige tijd bestond waarbij de buffermechanismen in gang zijn gezet en de zuurstofsaturatie van de hersenen is hersteld. Elektrische activiteit van het brein was verminderd tijdens een acute stijging in $etCO_2$ van tenminste 5mmHg. Deze respons lijkt versterkt tijdens ernstige hypercapnie, te zien aan een inhibitie van het achtergrondpatroon.

Een van de meest gebruikte medicijnen in de neonatologie is coffeïne, ter preventie van apneus van de vroeggeborene. Een apneu is een tijdelijke onderbreking van de ademhaling, iets wat vaak voorkomt in te vroeg geboren neonaten. De incidentie is direct gerelateerd aan de zwangerschapsduur.[20] In **deel IV** zijn de effecten van coffeïne op het neonatale brein geanalyseerd. Coffeïne kan gemakkelijk de bloed-hersen barrière passeren, door lipofiele eigenschappen. In het brein werkt coffeïne als een adenosine receptor antagonist door te binden aan de adenosine A1 en A2 receptoren.[21-23] Adenosine is een remmende neurotransmitter.

De CAP trial (caffeine for apnea of prematurity) is een grote studie die de effecten van coffeïne met placebo heeft vergeleken in vroeggeborenen.[24] Deze studie heeft eenpotentieel beschermend effect van coffeïne op de hersenen aangetoond, waarbij de kinderen met coffeïne een lagere mortaliteit hadden, een hogere overleving zonder neurologische beperking en een lagere incidentie van cerebrale parese. In **hoofdstuk 11** zijn de effecten van coffeïne ter preventie van apneus op het neonatale brein geanalyseerd in 34 te vroeg geboren neonaten, waarbij zowel de zuurstofvoorziening als elektrische activiteit van het brein zijn geanalyseerd. Daarnaast is doorbloeding van de hersenen beoordeeld met een

echo-Doppler onderzoek voor en na toediening van coffeïne, en is de pCO_2 uit bloedgas analyses voor en na coffeïne met elkaar vergeleken. De zuurstofsaturatie in het brein nam af met een toename in zuurstofextractie na coffeïne toediening, met een piek op 1 uur na toediening. Tegen verwachting in nam de doorbloeding van de hersenen iets af. Dit werd mogelijk veroorzaakt door het vaatvernauwende effect van coffeïne, dat met name komt door remming van de vaatverwijdende effecten van adenosine. Een alternatieve verklaring is de daling in pCO_2 na coffeïne. Elektrische activiteit van het brein was niet aangedaan door coffeïne, waaruit blijkt dat de lichte daling in de doorbloeding geen ernstige effecten op hersenfunctie had. Zowel de hartfrequentie als de gemiddelde arteriële bloeddruk namen geleidelijk toe na coffeïne.

Conclusie

De zuurstofsaturatie van de hersenen in de vroeggeborene staat onder de invloed van verschillendefactoren. Arteriële zuurstof saturatie is niet altijd een representatieve weergave van zuurstofsaturatie in de hersenenen. Het monitoren van de zuurstofsaturatie in het brein met near-infrared spectroscopy is daardoor van toegevoegde waarde in de neonatologie. Hiermee wordt op een directe en continue wijze inzicht in de zuurstofvoorziening en doorbloeding van de hersenen verschaft.

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Abbreviations
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Abbreviations

aCCS	Antenatal corticosteroids
aEEG	Amplitude integrated electroencephalography
AGA	Appropriate for gestational age
ANOVA	Analysis of variance
AOP	Apnea of prematurity
aOR	Adjusted odds ratios
BPAP	Bi-level positive airway pressure
BS	Burst suppression
BS+	Dense burst suppression
BS-	Sparse burst suppression
BSITD-III-NL	Bayley scales of infant and toddler development, third (Dutch) edition
BW	Birthweight
BPD	Bronchopulmonary dysplasia
CBF	Cerebral blood flow
CI	Confidence interval
cGMP	Cyclic guanosine monophosphate
CO	Carbon monoxide
CO_2	Carbon dioxide
COHb	Carboxyhaemoglobin
CPAP	Continuous positive airway pressure
CRIB-II	Clinical risk index for babies version II
cUS	Cranial ultrasound
DNV	Discontinuous normal voltage
eCS	Emergency caesarean section
EEG	Electroencephalography
etCOc	End-tidal carbon monoxide (corrected for CO in ambient air)
$etCO_2$	End-tidal carbon dioxide
FiO_2	Fraction of inspired oxygen
FT	Flat trace
FTOE	Fractional tissue oxygen extraction
GA	Gestational Age
Hb	Haemoglobin
HFOV	High-frequency oscillatory ventilation
HHb	Deoxygenated haemoglobin
HIE	Hypoxic-ischaemic encephalopathy
HR	Heart-rate
hsPDA	Hemodynamically significant patent ductus arteriosus
ISI	Inter-spontaneous activity transient-interval
ISP	ISI percentage
IQ	Intelligence quotient
IQR	Inter-quartile range
IVH	Intraventricular Haemorrhage
LA/Ao ratio	Left atrium to aorta ratio
LED	Light-emitting diode
LPAed	Left pulmonary artery end diastolic flow
M-ABC-2	Movement assessment battery for children 2nd edition
MABP	Mean-arterial blood pressure
Max	Maximum
MED	Indomethacin treatment
Min	Minimum
MRI	Magnetic resonance imaging
NDO	Neurodevelopmental outcome
NEC	Necrotising enterocolitis
NICU	Neonatal intensive care unit
NIRS	Near-infrared spectroscopy
NO	Nitric oxide
Non-sPDA	Hemodynamically non-significant patent ductus arteriosus
NoTREAT	No treatment
Ns	Not significant
O_2Hb	Oxygenated haemoglobin
PA	Postnatal age
PA-sq	The square of postnatal age, for modelling time
$paCO_2$	Arterial carbon dioxide tension
PIVH	Peri-intraventricular haemorrhage
PG E_2	Prostaglandin E_2
PMA	Postmenstrual age
ppm	Parts per million
pPROM	Preterm premature rupture of membranes
PS	Percentile score
PVL	Periventricular leukomalacia
RDS	Respiratory distress syndrome
SafeBoosC	Safeguarding the brains of our smallest children
SD	Standard deviation
SURG	Surgical ligation of a patent ductus arteriosus
$rScO_2$	Regional cerebral oxygen saturation
SaO_2	Arterial oxygen saturation

SAT	Spontaneous activity transient
SATrate	SATs per minute
SC hsPDA	Successfully closed hemodynamically significant PDA
SES	Socioeconomic status
SGA	Small for gestational age
SIMV	Synchronised intermittent mandatory ventilation
SRS	Spatially resolved spectroscopy
SRT	Surfactant replacement therapy
SVC	Superior vena cava
tHb	Total haemoglobin
TOHOP	Treatment of hypotension of prematurity
TREAT	Treatment
UC hsPDA	Unsuccessfully closed hemodynamically significant PDA
WPPSI-III-NL	Dutch Wechsler Preschool and Primary Scale of Intelligence 3rd Edition
WMI	White matter injury

Co-authors

Niek E. van der Aa, MD, PhD, Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

Thomas Alderliesten, MD, PhD, Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

Peter Andriessen, MD, PhD, Department of Neonatology, Máxima Medical Centre, Veldhoven, the Netherlands and Department of Pediatrics, Faculty of Health, Medicine and Life Science, University of Maastricht, The Netherlands

Willem Baerts, MD, PhD, Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

Frank van Bel, MD, PhD, Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

Cornelie A. Blok MD, Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

Johannes M.P.J. Breur, MD, PhD, Department of Cardiology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

Alexander Caidedo Dorado, MSc, PhD, Department of Electrical Engineering - STADI-US Center for Dynamical Systems, Signal Processing and Data Analytics, KU Leuven, Leuven, Belgium; Medical Information Technologies Department, iMinds, Leuven, Belgium

Emily Cohen, MD, Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands and The Ritchie Centre, Hudson Institute of Medical Research and Department of Paediatrics, Monash University, Melbourne, Australia

Koen P. Dijkman, MD, Department of Neonatology, Máxima Medical Centre, Veldhoven, The Netherlands

Floris Groenendaal, MD, PhD, Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

Ingrid C. van Haastert, MA, PhD, Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

Sabine Van Huffel, PhD, Department of Electrical Engineering - STADIUS Center for Dynamical Systems, Signal Processing and Data Analytics, KU Leuven, Leuven, Belgium; Medical Information Technologies Department, iMinds, Leuven, Belgium

Corine Koopman-Esseboom, MD, PhD, Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

Tanette G. Krediet, MD, PhD, Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

Petra M.A. Lemmers, MD, PhD, Department of Neonatology, Wilhelmina Children's Hospital and Brain Center Rudolf Magnus, University Medical Center Utrecht, The Netherlands

Mirella, M. C. Molenschot, MD, Department of Cardiology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

Gunnar Naulaers, MD, PhD, Department of Neonatology, University Hospital Gasthuisberg, Leuven, Belgium.

Renske Schappin, PhD, Department of Medical Psychology and Social Work, Wilhelmina Children's Hospital, University Medical Center Utrecht, the Netherlands

Mona C. Toet, MD, PhD, Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, the Netherlands

Moniek S. Veldhuis, MD, Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

Daniel C. Vijlbrief, MD, PhD, Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

Hendrik J. Vreman, PhD, Neonatal and Developmental Medicine Laboratory, Department of Pediatrics, Stanford University School of Medicine, Stanford, California, USA

Linda S. de Vries, MD, PhD, Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

Willem B. de Vries, MD, PhD, Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

Lauren C. Weeke, MD, Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

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Clinical Applications of Near-Infrared Spectroscopy. Petra Lemmers, Laura Dix, Gunnar Naulaers, Frank van Bel. In: Neonates in Hemodynamics and Cardiology: neonatology questions and controversies. C. Kleinman and I. Seri. Chapter 8. Elsevier Health Sciences, 2017.

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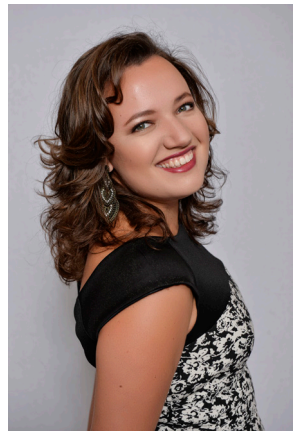
Curriculum Vitae



Laura Marie Louise Dix is op 18 augustus 1988 geboren te Leiden. Na het behalen van haar VWO diploma aan het Veenlanden College te Mijdrecht, gaat ze in eerste instantie Biomedische Wetenschappen studeren aan de Vrije Universiteit te Amsterdam. Een jaar later in 2007, mag ze na het succesvol doorlopen van de decentrale selectie alsnog beginnen aan de studie Geneeskunde bij dezelfde universiteit. Tijdens de bachelor Geneeskunde rondt ze ook de bachelor Biomedische Wetenschappen af. In 2014 studeert zij af als arts.

Middels de wetenschappelijke stage komt ze in 2011 bij de afdeling neonatologie van het Wilhelmina kinderziekenhuis terecht. Onder supervisie van Dr. P. Lemmers en Prof. Dr. F. van Bel begint hier het onderzoek met neonaten. De samenwerking bevalt goed, en in 2014 begint ze alhier aan haar promotietraject, met als focus: cerebrale oxygenatie bij vroeggeborenen.

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